Congenital Cystic Adenomatoid Malformation Type II with Associated Cardiac Anomalies

Mary Jane B. Carias, MD, Marissa Orillaza, MD

Many congenital anomalies of the lung in childhood have been described. Included is Congenital Cystic Adenomatoid Malformation also known as Congenital lobar Adenomatosis, Adenomatoid Hamartoma, Pulmonary Adenoma, and Congenital Bronchiolar Malformation in some literature.5 There are nine cases of CCAM diagnosed at the Philippine Heart Center since its establishment. Two of these are rare in as much as they also had associated cardiac anomalies. The first case has an associated Total Anomalous Pulmonary Venous Connection to the Superior Vena Cava and Atrial Septal Defect secundum type while the second case has Atrial Septal Defect, primum type. Both patients underwent lobectomy. The first case also underwent correction of the cardiac anomaly. Both patients were discharged improved. The objective of this paper is to present and describe two unique cases of CCAM with coexisting congenital heart disease in children admitted at the Philippine Heart Center. *Phil Heart Center J 2007;13(2):161-167.*

Key Words: Congenital Cystic Adenomatoid Malformation ■ Congenital heart disease

Congenital Cystic Adenomatoid Malformation of the lung is a multicystic non-functional lung mass accounting for 25% of all congenital lung malformation.[1] Its exact pathogenesis is still uncertain although latest literatures state it is due to fetal maldevelopment of the lung bud between the 6th to 8th weeks of gestation.[2] CCAM has no racial or sexual predilection, although some studies state it is more common in males. It is limited to a single lobe in 95% of cases and bilateral in less than 2% of cases.[3] Eighty percent (80%) are diagnosed before two years of age. The spectrum of this anomaly ranges from asymptomatic lesion to pulmonary compromise. CCAM is usually isolated but in about 10% of cases4 there are associated anomalies, hence, early detection of this entity is very crucial because its prognosis often depends upon the severity of the associated anomaly. Thus, the objective of this paper is to present and describe two unique cases of CCAM with coexisting congenital heart disease in children admitted at the Philippine Heart Center.

Case 1.

The first case is of a one-year old Filipina who presented with dyspnea and cyanosis. She was born preterm to a 32 year old G1P0 mother via caesarean section secondary to myoma uteri. She was tachypneic and dyspneic at birth but was acyanotic. She was confined after birth for two weeks for prematurity and sepsis. She presented with recurrent dyspnea and circumoral cyanosis at three months of age prompting consult with a pediatric cardiologist. Chest X-ray done showed cystic lucencies and bronchopneumonia at the right lower lung (Fig. 1). Chest CT Scan done showed bullous formation at the right lung and shunt anomaly with aberrant vessel connecting to the SVC. Two-dimensional echocardiography revealed Total Anomalous Pulmonary Venous Connection (TAPVC) to the superior vena cava and Atrial Septal Defect (ASD) secundum type. The patient was admitted as a case of Congenital Heart Disease, TAPVC to SVC, ASD secundum type, Bullae right lung field.

On the 13th hospital day, TAPVC correction, ASD patch closure and right lower lung lobectomy were performed. The submitted specimen for histopathology consisted of a spongy lung tissue measuring 8.5 x 2.5x 1 cm with multiple cysts, the largest measuring 2.1 x 2.5 cm (Figure7). Microscopically, it has bronchiolar – like cystic structures lined by ciliated columnar to cuboidal cells (Figure 10). These findings are compatible with Cystic Adenomatoid Malformation of the lung Type II. She was discharged improved and had latest OPD follow – up at 2 years of age, wherein her physical examination was essentially normal except for a faint murmur.

Case 2.

The second case is of a 21 days old boy who presented with dyspnea. He was born to a 34 year old G4P3 (3003), full term via normal spontaneous delivery. At birth, there was note of weak cry and spontaneous respiration.

On his second day of life, patient was noted to have interrupted feeding, tachypnea and severe chest indrawing associated with circumoral cyanosis especially during crying. Due to progressive dyspnea and cyanosis, consideration of a congenital heart disease was made

Accepted paper for PHC 15th Annual research Paper Competition 2007 and for 38th PHA Annual Convention held on May 16-18, 2007 at Edsa Shangrila Hotel, Philippines

Correspondence to Mary Jane B. Carias, M.D. Division of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

upon consultation with a pediatrician. Chest radiograph done revealed cystic lucencies at the right lung with mediastinal structures pushed to the left (Figure 3). He was eventually admitted at East Avenue Medical Center and was placed on mechanical ventilation due to severe dyspnea and cyanosis. He was transferred to the Philippine Heart Center where 2D Echocardiography done showed Atrial septal Defect (ASD), primum type.

On his second hospital day, he underwent right upper lobectomy where intraoperatively, there was a 10 x 8 x 6 cm cystic mass at the right upper lobe occupying almost half of the right hemithorax. The specimen submitted for histopathology revealed a spongy lung lobe with thinned out parenchyma. Cut sections show variably sized cystic spaces, the largest measuring 2.5 x 2.9 cm in diameter. Microscopically, the cysts resemble dilated thin- walled bronchioles separated by normal alveoli (Figure 12). It was signed out as Congenital Cystic Adenomatoid Malformation type II.

On the 5th post-operative day, the patient was extubated but eight hours later, he developed severe tachypnea. He was reintubated and chest tubes were inserted to evacuate hemothorax.

On his 8th post–operative day, patient developed sepsis secondary to ventilator-associated pneumonia. The pneumothorax however was resolved, so the chest tubes were removed. Repeat chest radiograph showed persistence of cystic lucency at the right middle lobe. Abdominal UTZ was done with unremarkable result.

On his 19th post-operative day, he underwent right middle lobectomy, which he tolerated. The specimen submitted for histopathology showed cystic spaces lined by ciliated columnar cells compatible with Congenital Cystic Adenomatoid Malformation Type II (Figure 11). He did not however undergo cardiac anomaly correction. He was discharged improved but was lost to follow–up.

Discussion

CCAM was first described in 1949 by Chin and Tang, but it was Stocker et al. in 1977 who proposed its first classification based upon clinical, gross pathologic and histologic features.6 (Table 1) Stocker has more recently expanded the classification into 5 types7 (Table 2) on the basis of the resemblance to normal anatomical structures from proximal to distal. Internationally, there is only 1 case out of 25,000 – 35,000 births, with only 58 cases seen in an eight year study done in England.8 The US, however, has no data available regarding its frequency. Thorpe – Beeston et al studied 132 cases of CCAM and found that 12% of cases had associated major malformations, and from these 3% had associated cardiac defects.[9] Locally, only two cases were diagnosed with CCAM at the Philippine Children's Medical Center and nine at the Philippine Heart Center. Congenital Cystic Adenomatoid Malformation is seen in the first two years of life in 80% - 85% of cases, [10] but it has also been reported in adults. Although the pathogenesis is still uncertain, it has been postulated that cellular bronchial atresia is the primary event11 while others believe that it is due to maldevelopment of the lung bud in the fetus.

Literatures have conflicting opinions about the association of CCAM and chromosomal abnormalities. While Nyberg, et al. pointed out that CCAM Type II appears to be more associated with other fetal abnormalities and aneuploidy, a recent review of 18 cases of CCAM (9 of whom demonstrated CCAM Type II) by Dumez et al did not reveal a single abnormal karyotype.[12] CCAM is not known to be associated with exposure to teratogens.[13]

CCAM most commonly present with respiratory distress due to the expanding cystic lung mass while others are asymptomatic and later discovered on chest radiograph. Cough, fever, and repeated respiratory infections are the less common presentations. CCAM has no preference for location.[14] Any lobe maybe affected with the following commonly affected in decreasing order of frequency: left lower lobe (LLL), left upper lobe (LUL, right lower lobe (RLL), and right upper lobe (RUL). Some later studies however have observed predilection of the right lung over the left lung for this anomaly.[15] Grossly and microscopically, CCAM presents as cysts of variable sizes composed of terminal respiratory structure of variable sizes which are lined by cuboidal or ciliated columnar epithelium. Table 1 shows the old classification of CCAM by Stocker which is still being used by some researchers in the latest literatures.

Table 1. Comparison of the Three Tyoes of CCAM

CHARACTERISTICS	CCAM Type1	CCAM Type 2	CCAM Type 3
Frequency (%)	75	10 – 15	10
Associated anomalies (%)	8	56	Nil
Cyst size (cm)	3 – 10	0.5 – 3	< 0.5
Mediastinal shift	(+)	Less common	(+)
Predominant epithelium	Ciliated pseudostratified columnar epithelium	Ciliated columnar and cuboidal epithelium	Cuboidal epithelium (minimal ciliation)
Mucous cells	32 %	Nil	Nil
Cartilage	10 %	Nil	Nil
Striated muscle	Nil	12 %	Nil
Presence of intervening pulmonary parenchyma	Yes	Yes	No
Prognosis	Good	Poor	Poor

*Old classification

Recently, Stocker expanded the classification of CCAM mainly based on its resemblance to normal anatomical features.

Table 2. Extended Classification of CCAM by Stocker

Type	Proportional incidence	Gross Appearance	Microscopy	Other features
0 (Bronchial type)	1 – 3 %	Solid; the lungs are small and firm throughout	Bronchial type airways that have cartilage, smooth muscle, and glands that are separated by abundant mesenchymal tissue	Neonates; other malformations; poor prognosis
1 (Bronchial /Bronchiolar type)	60 – 70 %	Large cysts (up to 10 cms.)	The cysts are lined by pseudostratified ciliated cells that are often interspersed with rows of mucous cells	Presentation maybe late; resectable; good prognosis; rare cases show carcinomatous change
2(Bronchiolar)	10 – 15%	Sponge- like composed of multiple small cysts (up to 2 cms) and solid pale, tumor like tissue	The cysts resemble dilated bronchioles separated by normal alveoli; striated muscle in 5%	Neonates; other malformations; poor prognosis
3 (Bronchiolar/ alveolar duct)	5%	Solid	There is an excess of bronchiolar structures separated by air spaces that are small, have a cuboidal lining, and resemble late fetal lung	Neonates; poor prognosis
4 (Peripheral)	15%	Large cysts (up to 10 cms)	The cysts are lined by a flattened epithelium resting on loose mesenchymal tissue	Neonates and infants; good prognosis

Type 0 (most rare) is composed of bronchial-like structures, separated by mesenchymal tissue. It is incompatible with life.[16] Type 1, the large cyst category, presents as a single large cyst frequently with much smaller cyst in the background (Figure 5). It is lined by pseudostratified columnar ciliated epithelium overlying a prominent fibromuscular layer (Figure 8). It is the most common and has the best prognosis.

Type 2 is composed of smaller cysts (Figure 6). It is difficult to distinguish where Type 2 CCAM ends and normal parenchyma begins. The larger cysts are lined by cuboidal to columnar cells; however, most of the lesion is composed of thin–walled bronchiole–like structures (Figure 9). Both the cases presented are comparable with the gross and microscopic description of CCAM Type II (Figure 13). In about 10% of cases, there are associated malformations. Renal anomalies (bilateral renal agenesis), abdominal wall anomalies, CNS defects (hydrocephalus), gastrointestinal anomalies (diaphragmatic hernia, jejunal atresia, tracheoesophageal fistula), and cardiac anomalies and anomalies of the great vessels (VSD, TOF, Truncus arteriosus) are the anomalies associated with CCAM Type II.[16] Of the latest literatures, only one case of CCAM Type II with associated VSD, ASD, and Transposition of the Aorta was reported. This was a case of a patient with Trisomy 18 associated with CCAM Type II.[12] There is no reported case of an associated TAPVC yet. Type II has a worse overall outcome compared to Type I.

Type 3 is the most solid variant. The cysts are innumerable and evenly distributed. They tend to occupy the entire lobe or most of one lung. The microscopic appearance is suggestive of immature lung. It is rare and it carries a poor prognosis due to the hypoplasia frequently involving the other lung segments.

Type IV is a large cyst in the periphery of the lung which is lined by flattened pneumocytes. [17] It has a good prognosis. It is crucial to diagnose the exact type of malformation in order to exclude associated anomalies, as well as the risk of development of malignancy later in life. The two cases presented have clinical and histopathologic findings compatible with CCAM Type II (Table 3).

Table 3. Type II CCAM Compared with The Two Cases

Characteristics	CCAM Type II	Case 1	Case 2
Cyst size (cm)	0.5 – 3	2.5 x 1	2.9 x 2.5 2.9 x 2.5
Associated Anomalies	Yes	TAPVC to SVC ASD, secundum type	ASD, primum type
Mediastinal Shift	Yes	None	Yes
Predominant Epithelium	Ciliated Columnar and Cuboidal Epithelium	Ciliated Columnar and Cuboidal Epithelium	Tall Columnar Epithelium
Cartilage	Nil	None	None
Presence of Intervening Lung Parenchyma	Yes	Yes	Yes
Mucous Cells	Nil	None	None
Prognosis	Poor	Last followed up at 2 years of age	Lost to follow – up

Imaging studies provide a crucial role in the diagnosis of CCAM. Chest X-ray is included in the basic work-up of the child with suspected CCAM. It identifies CCAM of sufficient size to cause clinical problems. The usual appearance is of a mass containing air–filled cysts.[20] (Figure 2) Other radiological signs that maybe evident in

clude mediastinal shift, pleural and pericardial effusions, and pneumothoraces. The two cases presented both had X-ray results fulfilling the radiologic signs of CCAM.

Chest CT scan provides a rapid means of defining the extent of CCAM in all age groups. The typical appearance is of multilocular cystic lesion with thin walls surrounded by normal lung parenchyma.[6] (Figure 4) CT scan of the chest may also outline additional coexisting lesions. In the first case presented, the associated cardiac lesion was appreciated with CT Scan.

MRI is particularly useful in the diagnosis of CCAM. The appearance of the lesion on MRI is determined by the size of the lesion as well as the number and size of the cysts.[20] CCAM usually demonstrates some degree of inhomogeneity due to the multiple cysts. Antenatal UTZ can diagnose CCAM prenatally; however, it cannot distinguish it clearly from other lung lesions such as pulmonary sequestration or lobar emphysema.[20] It is mandatory to perform renal and cerebral UTZ in all newborns with CCAM in order to exclude coexisting renal and CNS anomalies. Echocardiography is also performed in all infants with CCAM to rule out any coexisting cardiac lesions.[20] The two cases presented were referred to PHC primarily due to their coexisting cardiac lesions seen on Echocardiography.

In any child presenting with dyspnea, CCAM is always a strong consideration. However, its signs and symptoms are constitutional and maybe present in other cystic lung diseases. Pulmonary sequestration is among the most common differential diagnosis of CCAM. It is a mass of abnormal lung tissue that does not communicate with the tracheobronchial tree through a normally connected bronchus, and receives its own blood supply from a systemic artery.[18] Congenital Lobar Emphysema is another consideration. This is a localized area of emphysema that presents in early infancy as respiratory distress. Histologically, the parenchyma shows non-specific distention. Bronchogenic cyst is another consideration which is commonly found in the anterior mediastinum or around the hilum. Grossly, the cysts are unilocular , maybe up to 10 cms in diameter and are not in communication with the tracheobronchial tree.[19] Lung abscess is a less common differential diagnosis. It may be difficult to distinguish from any type of lung cyst; however, an abscess often has multiple bronchial communications. Surgical intervention remains the mainstay of therapy for CCAM. The surgical options include fetal surgery, postnatal surgical approaches, and termination of pregnancy. If left untreated, patient can develop pneumothorax, hydrothorax, and recurrent pneumonia leading to demise of the patient. Malignant changes such as rhabdomyosarcoma, pulmonary blastoma, bronchioalveolar carcinoma, and squamous cell carcinoma have also been reported later in life. No specific medical treatment is described for CCAM.[20] Antibiotics are given to children with CCAM complicated by pneumonia. Respiratory support ranging from O2 supplementation to mechanical ventilation maybe required for neonates with respiratory distress. The overall size of the lesion has also been reported as being an important predictor of survival, and one study show 10% to 20% of cases of CCAM can shrink and may even disappear in utero during the 3rd trimester.[21] Poor prognosis is commonly associated with presence of associated anomalies, bilateral lesions, and microcystic lesion. In the absence of any known risk factor, no advice regarding pre-pregnancy preventive measures can be provided. Like with any other child, smoking by and around a child with CCAM is to be avoided.

Table 4. Case Summary of the Two Cases

Case	1	2
Age	1 year old	21 days old
Sex	F	M
Mode of Delivery	CS due to myoma uteri	NSVD
Age of Gestation Completed	Preterm	Full term
Presenting Symptom	Dyspnea	Dyspnea
Lung Involved	RLL	RUL, RML
Associated Cardiac Anomalies	TAPVC to SVC ASD, secundum type	ASD, primum type
Size of Cyst (cm)	2.1 x 2.5	2.9 x 2.5 2.9 x 2.5
Mediastinal Shift	(-)	(+)
Treatment Done	Right Lower Lobe Lobectomy TAPVC Correction	Right Upper Lobe Lobectomy Right Middle Lobe Lobectomy

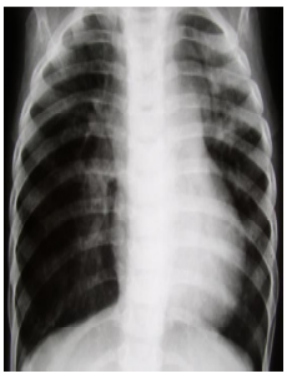


Figure 1. Chest Radiograph of Case 1 showing cystic lucencies in the right lung field

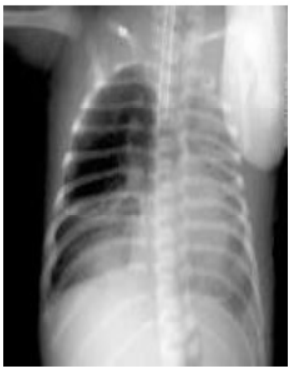


Figure 2. Chest Radiograph of a patient with CCAM. Note the mass containing air – fluid cysts

Conclusion

Congenital Cystic Adenomatoid Malformation, however rare, presents with constitutional signs and symptoms comparable with the more common disease entities. Although rare, it should be entertained in a child who presents with dyspnea and cystic lesion in chest x-ray. Table 4 summarizes the two cases that both presented with dyspnea. With clinical suspicion, radiologic work ups and histopathologic efforts, the more complex anomalies were identified and given proper treatment. Due to the rarity of the reported cases of CCAM Type II, some of the cases may not fit the prototype, yet will still fall under its classification. With early access to imaging modalities and accurate histopathology, cases of CCAM Type II with cardiac anomalies maybe higher than previously reported.

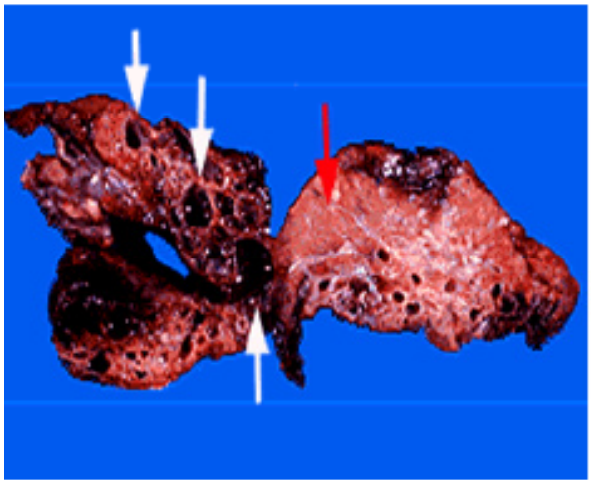


Figure 6. CCAM Type II showing multiple smaller cysts

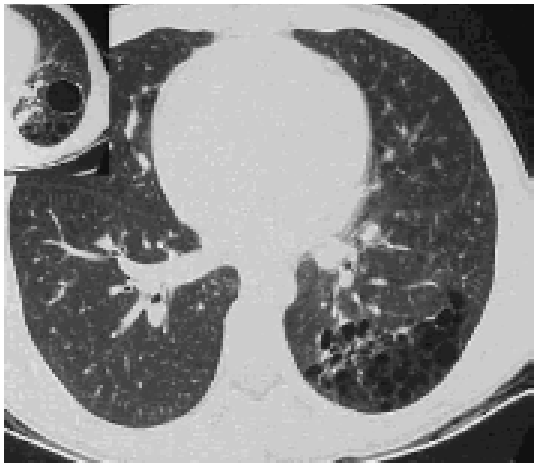


Figure 4. CT Scan of CCAM showing multilocular cysts with thin walls

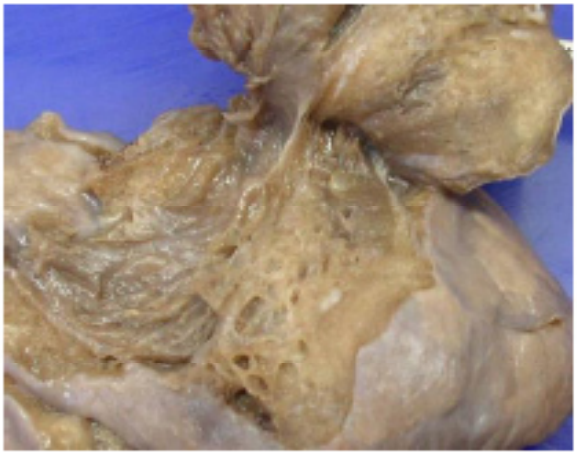


Figure 7. Gross specimen on Case 1 showing multiple smaller cysts

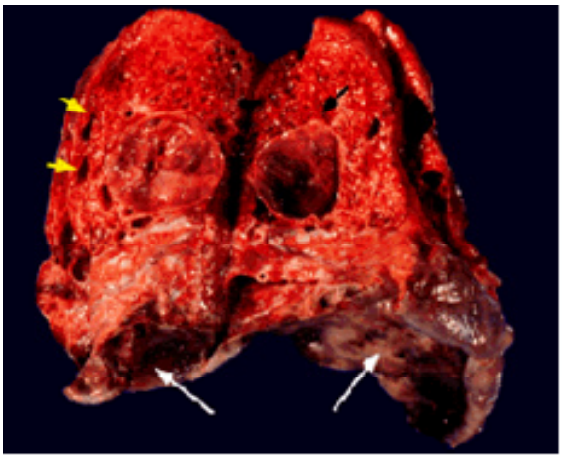


Figure 5. CCAM Type I showing a large cyst surrounded by smaller cysts

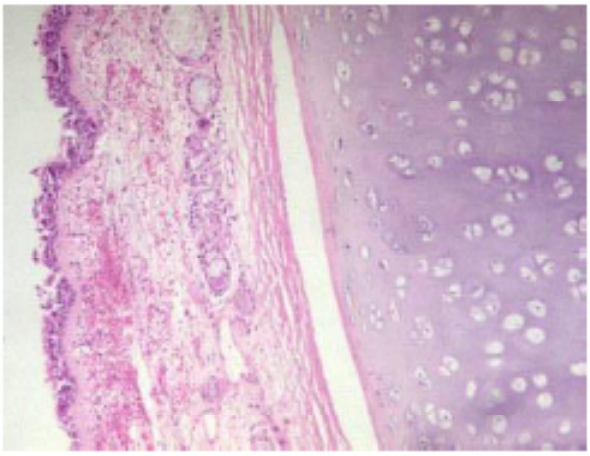


Figure 8. CCAM Type I lined by pseudostratified columnar epithelium and with prominent cartilage (10x magnification)

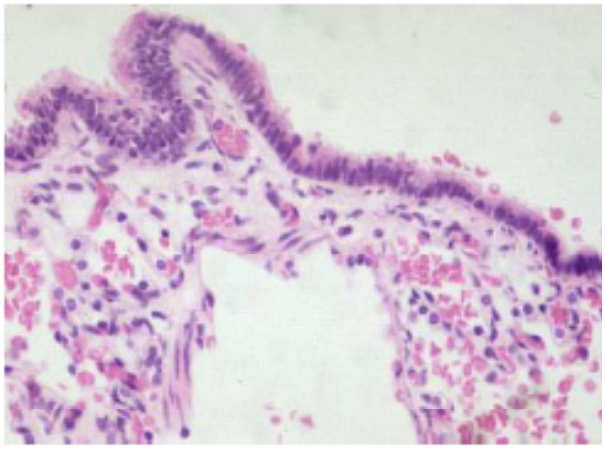
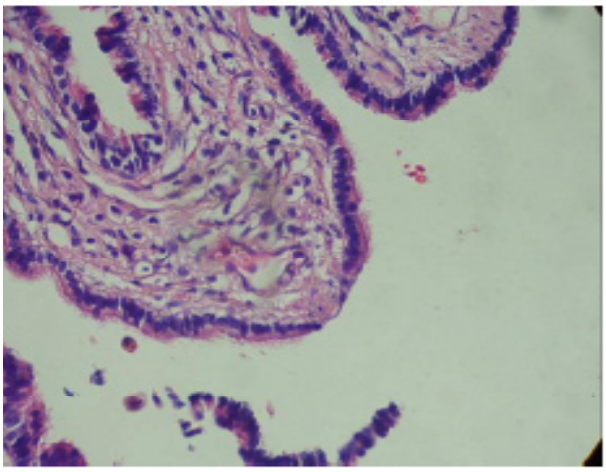


Figure 9. CCAM Type II showing cystic spaces lined by ciliated tall columnar cells (10x magnification)



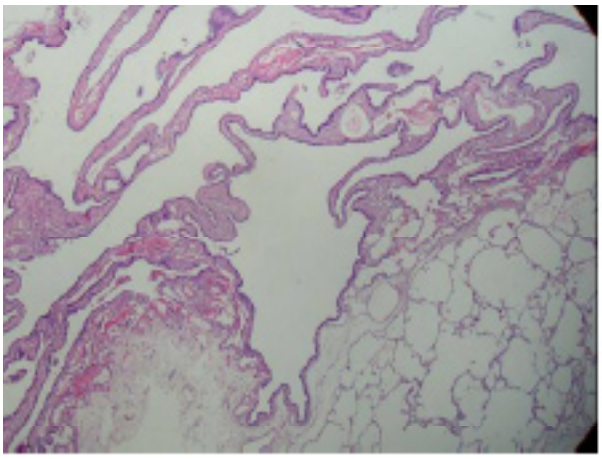


Figure 10. Case 1 showing cystic spaces lined by tall columnar to cuboidal cells (10x magnification)

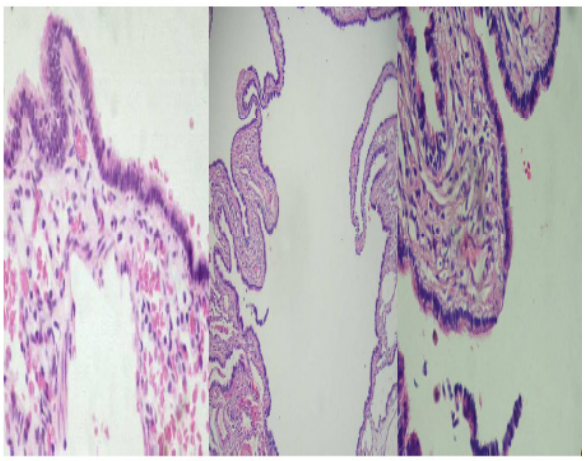


Figure 13. Microscopic Comparison of CCAM Type II and Case1 and 2

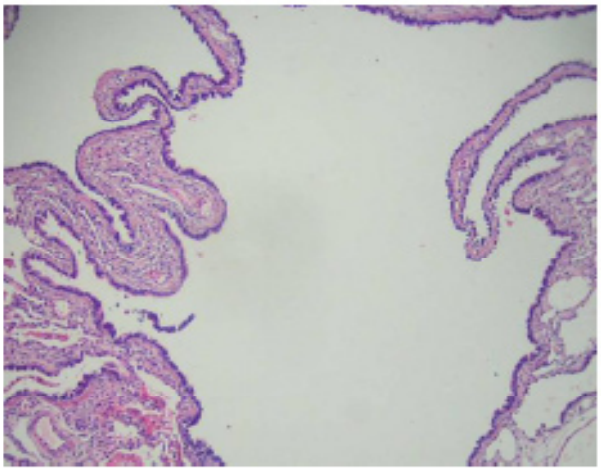


Figure 11. Case 2 taken from R Middle Lobe showing cystic spaces resending dilated bronchioles (10x magnification)

References

1. Vaugh David et al. CCAM of the Lung. EMedicine Journal. Sep7, 2001. Vol 2, Number 9.
2. Paskal Stucki, PICU, CHUV, http://www neonet. Ch//. Nov 2001
3. M. Van Leersun, et al. Prune Belly Syndrome with CCAM. Http.www eurorad journal org/case.
4. www. Elungdis. Com.CCAM.
5. www. THEFETUS.net CCAM Type III.
6. www.icondata.com.Cam.1994
7. Fergus Mac Sweeney, et al. An Assessment of the Expanded Classification of CCAM and their Relationship to Malignant Transformation
8. CCAM http://www emedicine.com/ped
9. Thorpe – Beeston JG, Nicolaides KH. Cystic Adenomatoid Malformation of the Lung: Prenatal Diagnosis, 1994 August; 14 (8); 677 – 688
10. Miller RK et al. CCAM of the Lung. A Report of 17 Cases and Review of Literature. Pathology Annual 1980; 158: 387 – 402

11. Levs C Tracer RS. CCAM. Respiratory Care. 2000, 42 (8):1112 – 1120
12. Mai Shipp. Trisomy 18 Associated with Type II CCAM. A\ Case Report. http//www ObGyn net/ns/cotm/June 1999.
13. Aleksandra Novakov Mikic, CAM,http.//www The Fetus net. 2000 – 05
14. Asim Kurjak, et al. CCAM Type III 1991.Kurjak www/The Fetus Net
15. Meenn Signh et al. CCAM of the Lung.http://www/Indian Pediatrics Net, Nov 2000
16. Scott J. Sheets. Bronchogenic cyst and CCAM. March 2003 . http//research netscape.com.
17. CPAM http://pathswsm 54.ucsf.edu/CTS
18. Elizabeth A. Stillwell, et al.CCAM of the Fetal lung.http:// www.sonocredit. july 25, 2000.
19. Philip S. Hasleton. Spencer's Pathology of the Lung. 1996. 69 – 71
20. Sittig SE, Asay GF. CCAM in the Newborn: Two Cases and Review of the Literature. PMID : (Pubmed)
21. Cincinnati Childrens' hospital Med Center. 1999 – 2004. http//www. Cincinnati Children.org.