ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

A Clinico pathological Study of Cystic Lung Lesions in Children and Prognostic Evaluation with Ki – 67 at Tertiary Care Hospital

[1]Dr. Nadera Sultana, [2]Dr. Sridevi P

[1]Assistant Professor, [2]Associate Professor, Department of Pathology, Ayaan Institute of Medical Sciences, Kankamidi, Telangana, India

Correspondence:
Dr. Sridevi P
Associate Professor, Department of Pathology, Ayaan Institute of Medical Sciences, Kankamidi, Telangana, India

ABSTRACT

Introduction: Congenital cystic lesions of the lung are uncommon but share similar embryologic and clinical characteristics. An overall incidence of congenital cystic lesions of the lung is 1/10,000 to 1/25,000 births (and 2.2% as compared to acquired lesions). Presentation varies from life-threatening symptoms at birth to incidental findings at autopsy. Diagnosis is either made in utero or due to complications of the lesion, such as lung abscess, pneumonia, or pneumothorax.

Materials and Methods: This is a prospective study conducted in the Department of Pathology at Ayaan Insitute of Medical Sciences, Kankamidi from January 2020 to December 2021. The present study was done to evaluate the demographic profile, clinical, radiological and histopathological findings of cystic lung lesions in children and to demonstrate efficacy of Ki 67 as a prognostic marker in predicting malignancy in these lesions. A total of 53 lobectomy specimens received and studied in the present study.

Results: Out of these 53 cases were lobectomy specimens of cystic lung lesions. Highest number of cystic lung lesions were observed in the left upper lobe. (23 cases) and the lowest number of cystic lung lesions were observed in the right upper lobe (3cases). Highest number of cystic lung lesions were Congenital lobar emphysema (52.83 %) and least number of cystic lung lesions were Bronchogenic cyst (5.66 %). Among all cystic lung lesions maximum cyst had size range between 0.5 to 2 cm. Immunohistochemical staining using Ki 67 showed a high proliferative index in 5 cases of CCAM. Remaining all 7 cases of CCAM and 2 cases each of Bronchogenic cyst, Intra lobar Sequestration and Congenital lobar emphysema had low proliferative index.

Conclusion

Conservative anatomic resections should be attempted to preserve functional lung tissue. Apart from initial stabilization, resection of lesion and careful histopathological examination and Immunohistochemistry with Ki 67 is necessary for detecting rare malignancies associated with lung cysts as early as possible. Children with increased Ki 67 expression in cystic lung lesion should be carefully followed up to detect occult malignancies associated with lung cysts.

Keywords: Cystic Lung Lesions, Ki – 67, Histopathological examination

INTRODUCTION

Congenital cystic lesions of the lung are uncommon but share similar embryologic and clinical characteristics. An overall incidence of congenital cystic lesions of the lung is 1/10,000 to 1/25,000 births (and 2.2% as compared to acquired lesions). [1] Presentation varies from life-threatening symptoms at birth to incidental findings at autopsy. Diagnosis is either made in utero or due to complications of the lesion, such as lung abscess, pneumonia, or pneumothorax. [2]

Cystic lung disease encompasses four categories of disease: bronchogenic cysts, cystic adenomatoid malformation, lobar emphysema, and pulmonary sequestration. Bronchogenic cysts arise from abnormal folding of tissue during fetal development. [3] Cystic adenomatoid malformations are benign, masses of abnormal lung tissue that generally occur in one side of the lung. [4] Lobar emphysema occurs when an obstruction in one lung lobe traps airflow. This trapped air stretches and expands the lung tissue, leading to cyst development. Pulmonary sequestration is a mass of lung tissue that is not connected to any airways and thus performs no function. The sequestration can be either inside or outside the lungs. [5]

Cysts were grouped as developmental, acquired, and pulmonary blebs and emphysematous bullae. It is often difficult to know whether a cyst is congenital or acquired. [6] Buntain and colleagues proposed a definition stating that a lung cyst is considered congenital if a similar pathologic picture can be found in the prenatal or immediate neonatal period before any postnatal traumatic or inflammatory insult, or if anomalous blood supply is present at the time of diagnosis. [7]

No definite known cause has been proposed, although there is interest in the role of some genes such as fatty acid binding protein-7 in the pathogenesis of CPAMs. The overlap and occasional coexistence of these cystic lesions suggest a possible single common pathologic mechanism for their development. [8] The level of the obstruction, the completeness of the obstruction, and the timing of the obstructive events together produce the different patterns of lung malformations seen. The exact mechanism by which obstruction or atresia bring about various final lesions have yet to be elucidated. These diseases may result from compromised interaction between embryologic mesodermal and ectodermal lung components during development. [9]

Most congenital lung cysts are diagnosed at the 20-week anomaly scan. The diagnostic accuracy is 100% for congenital cysts, but specificity for distinct lesions are variable. Doppler ultrasound may identify an abnormal vessel from the aorta to suspect pulmonary sequestration, but it cannot confirm hybrid (mixed) lesions. Large lesions may cause cardiac compression, resulting in hydrops foetalis and fetal demise. [10]

Bronchioloalveolar carcinoma (BAC) and rhabdomyosarcoma in association with CCAM have been reported in children and adults. These malignant transformations were noted in primary CCAM lesions and those that were incompletely resected. [11] The long-term malignant potential of in situ CCAMs has been further reported, suggesting postnatal surgical excision by means of lobectomy rather than segmentectomy as well as surgical preference to long-term radiological surveillance. Thus, with the increasing number of reports and case series of malignancy within CCAM, together with the possibility of lung infection, surgical resection in nearly all cases of CCAM is recommended. [12]

Ki-67 nuclear antigen is expressed in proliferating cells and expressed throughout the cell cycle (G1, S, G2, and M phases) but not in resting cells (G0). CCAM results from an imbalance between cell proliferation and programmed cell death. Increased cell proliferation in CCAM can be caused by overexpression of keratinocyte growth factor, a pneumocyte mitogen required for normal lung development. [13] Ki67 is a good prognostic marker predicting malignancy in cystic congenital adenomatoid malformation cases**.** An examination

of factors that control cell proliferation in Cystic lung lesions will provide further insight into the pathogenesis of these lesions.

AIMS AND OBJECTIVES

To correlate the clinical, radiological and histopathological findings of cystic lung lesions in children. To demonstrate the efficacy of Ki 67 as a prognostic marker in predicting malignancy in congenital cystic lung lesions.

MATERIALS AND METHODS

This is a prospective study conducted in the Department of Pathology at Ayaan Insitute of Medical Sciences, Kankamidi from January 2020 to December 2021. The present study was done to evaluate the demographic profile, clinical, radiological and histopathological findings of cystic lung lesions in children and to demonstrate efficacy of Ki 67 as a prognostic marker in predicting malignancy in these lesions. A total of 53 lobectomy specimens received and studied in the present study.

Congenital cystic lung lesions reported were retrieved from the pathology register and the histopathology slides were studied. The clinical details including the radiological and intraoperative findings were retrieved from hospital registers. All the clinical details including radiological findings as well as intraoperative findings were recorded. Paraffin embedded blocks of 53 cases were collected and Hematoxylin & Eosin stained sections were studied.

IMMUNOHISTOCHEMISTRY USING KI 67

18 cases of lung cyst showing hyperplasia and dysplasia of respiratory epithelium were processed for Ki 67 immunoexpression after routine histopathological examination. Micro sections of 4-5 µm thickness were prepared from the corresponding paraffin blocks on albumin coated slide for H & E staining and sections of 3 µm thickness were prepared on separate poly- L-lysine coated slides for immunohistochemical staining with Ki 67. Standard procedure for H&E staining was employed using Harris haematoxylin and aqueous Eosin.

RESULTS

The present study of cystic lung lesions in children was conducted at tertiary care referral centre. Out of these 53 cases were lobectomy specimens of cystic lung lesions.

Table 1: Age wise Distribution of cases

Cystic lung lesions	0-6 month	6-12 month	1-5 year	6-10 year	11-13 year
Bronchogenic cyst	-	1	1	1	-
Sequestration	4	-	-	-	-
Congenital lobar emphysema	21	1	4	2	-
CCAM	9	3	2	2	2
TOTAL	34	5	7	5	2

Highest number of cases were found in children below 6 months of age. 34 cases (64.15%) were seen in children below 6 months and only 2 cases (3.77%) in children of 11-13 years age group in table 1.

Table 2: Sex Incidence of cystic lung lesions

Sex	Number of children	Percentage
Males	33	62%
Females	20	38%
Total	53	100%

Cystic lung lesions predominated in the male children in our study with M:F ratio of 1.6 : 1 in table 2.

Table 3: Symptom wise distribution of cystic lung lesions

Symptoms	Bronchogenic cyst (n =3)		Sequestration (n= 4)		Lobar emphysema (n=28)		CCAM (n=18)	
	No of cases	%	No of cases	%	No of cases	%	No of cases	%
Shortness of breath	2	66.66%	1	25%	19	67.85%	12	66.66%
Cough	1	33.33%	2	50%	14	50%	10	55.55%
Fever	2	66.66%	1	25%	17	60.7%	12	66.66%
Respiratory distress	1	33.33%	2	50%	8	28.57%	4	22.22%

Most common symptom associated with cystic lung lesions was shortness of breath (64 %) in table 3.

Table 4: Cystic lung lesions diagnosed by radiology and imaging.

Cystic lung lesions	Chest X Ray		U/S Chest		MRI/CT SCAN	
	No of cases	%	No of cases	%	No of cases	%
Bronchogenic cyst (n =3)	1	33.33%	1	33.33%	2	66.66%
equestration (n= 4)	2	50%	1	25%	4	100%
obar emphysema (n=28)	7	25%	12	42.8%	22	78.57%
CCAM (n=18)	10	55.55%	11	61.1%	15	83.33%

Chest X ray, U/S chest and MRI/CT scan of chest was performed in most of the cases of cystic lung lesions. CT/MRI scan had the highest diagnostic accuracy in detecting cystic lung lesions in our study in table 4.

Table 5: Showing side of lobectomy in cystic lung lesions.

Cystic lung lesions	Right Upper Lobe	Right Middle	ht Lower Lobe	Left Upper Lobe	Left Lower Lobe
nchogenic cyst (n =3)	1	-	-	2	-
Sequestration (n= 4)	-	-	2	-	2
ar emphysema (n=28)	-	5	7	15	1
CCAM (n=18)	2	1	1	6	8
TOTAL (n=53)	3	6	10	23	11

Highest number of cystic lung lesions were observed in the left upper lobe. (23 cases) and the lowest number of cystic lung lesions were observed in the right upper lobe (3cases) in table 5.

Table 6: Distribution of cystic lung lesions according to histopathological type is as follows:

Cystic lung lesion	No of cases	Percentage
Bronchogenic cyst	3	5.66 %
Sequestration	4	7.54 %
Congenital lobar emphysema	28	52.83 %
ital cystic adenomatoid malformation	18	33.96 %
TOTAL	53	100 %

Highest number of cystic lung lesions were Congenital lobar emphysema (52.83 %) and least number of cystic lung lesions were Bronchogenic cyst (5.66 %).

Figure 1: Gross appearance of Bronchogenic cyst

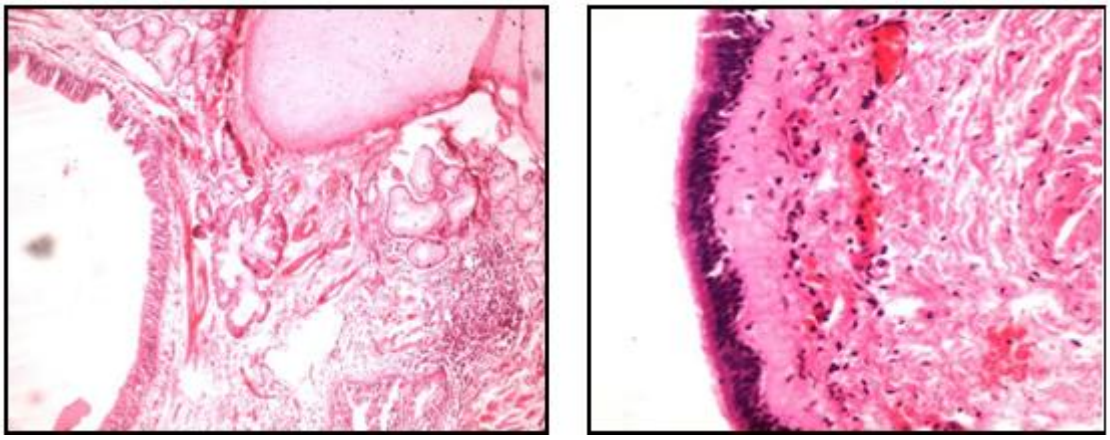

Figure 1a: H & E – 10 X **Figure 1b: H & E – 40 X**

Figure 2: Gross appearance of sequestration

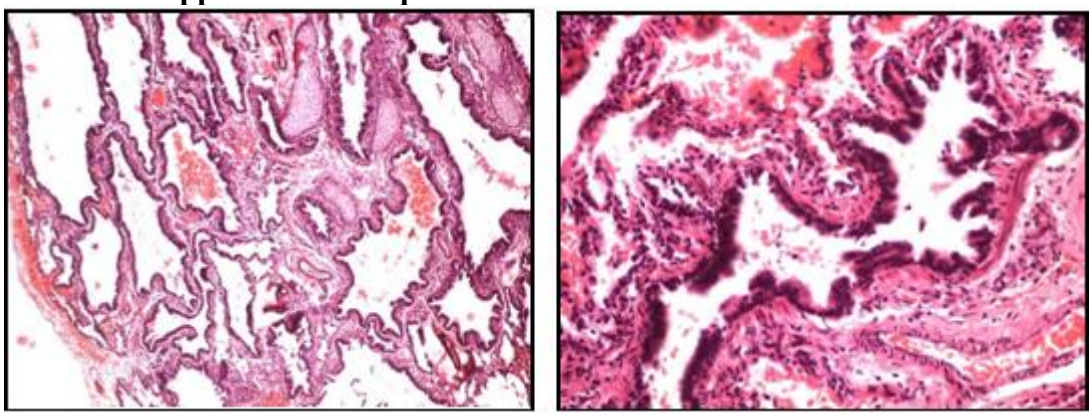

Figure 2a: H & E - 10 X **Figure 2b: H & E – 40X**

Table 7: Showing gross size of cystic lung lesions.

Cystic lung lesions	**< 0.5 cm**	**0.5 – 2 cm**	**> 2 cm**
Bronchogenic cyst (n =3)	-	1	2
Sequestration (n= 4)	2	2	
Lobar emphysema (n=28)	10	13	5
CCAM (n=18)	4	6	8
TOTAL	16	22	15

Among all cystic lung lesions maximum cyst had size range between 0.5 to 2 cm in table 7.

Table 8: Immunohistochemical Staining Using Ki 67 was performed in 18 cases.

Lung Cyst	**No of cases**	**High Ki 67 index**	**Low Ki 67 index**
Bronchogenic cyst	2	-	2 cases
Intra lobar Sequestration	2	-	2 cases
Congenital lobar emphysema	2	-	2 cases
Congenital cystic pulmonary malformation	12	5 cases [41.6 %]	7 cases [58.4 %]
TOTAL	18	5	13

Immunohistochemical staining using Ki 67 showed a high proliferative index in 5 cases of CCAM. Remaining all 7 cases of CCAM and 2 cases each of Bronchogenic cyst, Intra lobar Sequestration and Congenital lobar emphysema had low proliferative index.

Table 9: Showing the percentage of nuclear immunostaining with Ki 67 in each case.

LUNG CYST	H.P No	SUBTYPE	KI67 INDEX	RESULT
Bronchogenic cyst	560 / 12		4.5	LOW
	24 / 13		5.2	LOW
Intralobar sequestration	831 / 12		4.7	LOW
	297 / 13		5.6	LOW
Congenital lobar emphysema	436 / 11		4.3	LOW
	1051 / 12		4.8	LOW
Congenital cystic pulmonary malformation	133 / 11	CCAM I	19.5	HIGH
	176 / 11		18.8	HIGH
	375 / 11		19.7	HIGH
	30 / 12		4.2	LOW
	399 / 12		5.6	LOW
	757 / 12		16.2	HIGH
	1059 /12		18.6	HIGH
	64 / 11	CCAM II	6.8	LOW
	970 /12		5.4	LOW
	171 / 12	CCAM III	4.5	LOW
	716 / 12	CCAM IV	6.4	LOW
	355 / 13		5.2	LOW
TOTAL	18 CASES			

Among the 18 cases of cystic lung lesion showing hyperplasia and dysplasia of respiratory epithelium subjected for Ki 67 immunoexpression, Ki 67 showed a high proliferative index in 5 cases of Congenital cystic pulmonary malformation type 1.Congenital cystic pulmonary malformation type 2, 3and 4, Bronchogenic cyst, Intra lobar Sequestration and Congenital lobar emphysema had low proliferative index with Ki 67. Adjacent normal lung was taken as a positive control.

DISCUSSION

Cystic lung lesions present in the newborn period and early childhood with respiratory distress, and require prompt diagnosis with emergency surgical resection. The etiology of such lesions is controversial and many theories have been proposed. The cause of many of these malformations has been described as in-sequestration and foregut malformations, whereas that of others (e.g., CCAM and simple lung cyst) remain obscure. [14] During fetal lung growth, the timing of embryologic alterations, whether early or late, determines not only the type of lesion but also the severity of the malformations and its impact on overall lung growth. [15]

In our study, highest number of cystic lung lesions were observed in the left upper lobe (23 cases) and the lowest number of cystic lung lesions were observed in the right upper lobe (3cases). Lobar emphysema was more common in the left upper lobe, CCAM was more common in the left lower lobe, 2 cases of sequestration of intralobar type were seen in right lower lobe and 2 cases of Bronchogenic cyst involved left upper lobe and 1 case involved the right upper lobe. These findings were more or less similar to the study done by Coran AG et al (1994) [16]. In the study by Al- Bassam et al [1999], the left upper lobe was the commonest site for CLE followed by right middle lobe, in CCAM the lower lobes were equally affected, the bronchogenic cyst were centrally located in the majority of the patients and 5 cases of pulmonary sequestration were intralobar variety. [17]

In our study among all cystic lung lesions maximum cyst had size range between 0.5 to 2 cm. This was comparable to the study done by Al- Bassam et al [1999] in which most of the cyst

had size below 2 cm. [17] In our study highest number of cystic lung lesions were Congenital lobar emphysema (52.83 %) and least number of cystic lung lesions were Bronchogenic cyst (5.66 %) which were comparable with the other studies.

In our study among the 18 cases of cystic lung lesion showing hyperplasia and dysplasia of respiratory epithelium subjected for Ki 67 immunoexpression, Ki 67 showed a high proliferative index in 5 cases of Congenital cystic pulmonary malformation type 1. Congenital cystic pulmonary malformation type 2, 3 and 4, Bronchogenic cyst, Extra lobar Sequestration and Congenital lobar emphysema had low proliferative index with Ki 67. This is comparable to the study done by Cangiarella J et al (1995) in which Ki 67 IHC showed increased proliferative Index in all cases of CCAM. [18]

This reveals that there is increased cell proliferation in congenital cystic adenomatoid malformation of lung as compared to the normal lung. Children with increased Ki 67 expression in cystic lung lesion should be carefully followed up to detect rare malignancies associated with lung cysts. Increased proliferation index is associated with increase in the risk of malignant transformation. A life-long follow-up in those patients who had a resection of cystic lung lesion in early childhood is recommended as supported by the study done by van Koningsbruggen S et al (2001). [19]

Prognosis depends on the size of the lung mass and secondary physiologic derangement. A large cystic lung lesion causes mediastinal shift, hypoplasia of normal lung tissue and cardiovascular compromise. [20] Microcystic lesion and bilateral lung involvement highly correlated with poor prognosis as suggested by the study done by Bunduki et al (2000). [21]

Surveillance to detect an early transition in the character of a cystic lung lesion is important due to the possibility of Pleuropulmonary Blastoma, or other rare malignancies associated with lung cysts as suggested by the study done by Priest et al (2009). [22]

As CCAM can host metaplastic mucous cells, primitive mesenchymal cells and differentiated but poorly organized striated muscle fibers, it has been proposed that CCAM may act as a predisposing condition for oncogenesis as suggested by the study done by Cass DL et al (1998). [23] CCAM is caused by dysregulated paracrine growth of mature cells and extracellular matrices and that Glandular Component could have the potential for malignant transformation was suggested by the study done by Wang et al (1999). [24]

The possible development of malignancies justifies prompt resection shortly after diagnosis, even in asymptomatic patients. A life-long follow-up in those patients who had a resection of cystic lung lesion in early childhood is recommended as supported by the study done by van Koningsbruggen S et al (2001). [19]

CONCLUSION

Conservative anatomic resections should be attempted to preserve functional lung tissue. Apart from initial stabilization, resection of lesion and careful histopathological examination and Immunohistochemistry with Ki 67 is necessary for detecting rare malignancies associated with lung cysts as early as possible. Children with increased Ki 67 expression in cystic lung lesion should be carefully followed up to detect occult malignancies associated with lung cysts.

REFERENCES

1. Shamji F.M. Classification of cystic and bullous lung disease. Chest surgery clinics of North America 1995;5:701-716.
2. Hernanz-Schulman M. Cysts, and cystlike lesions of the lung. Radiol Clin N Am 1993;31:631-643.
3. Cheney G., Garland L.H. Pulmonary pneumocyst. Report of enormous solitary cyst in healthy adult female. Am J Med Sci 1938;196:699-703.

4. Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. Hum Pathol 1977;8:155 - 171.
5. Soosay G.N., Baudouin S.V., Hanson P.J.V., et al. Symptomatic cysts in otherwise normal lungs of children and adults. Histopathology 1992;20:517-522.
6. Langston C. New concepts in the pathology of congenital lung malformations. Semin Pediatr Surg 2003; 12(1):17–37.
7. Buntain W.L., Isaacs H., Payne V.C., Lindesmith G.G., Rosenkrantz J.G. Lobar emphysema,cysticadenomatoid malformation,pulmonary sequestration, and bronchogenic cyst in infancy and childhood: a clinical group. J Pediatr Surg 1974; 9 :85-93.
8. Warren H.Lewis, CHAPTER Xl, Splanchnology,Respiratory apparatus .In : Gray,s Anatomy Of Human Body,20th edition, Philadelphia. USA: Lea & Febiger;2012.p. 1071.
9. Warren H.Lewis, CHAPTER Xl, Splanchnology,Respiratory apparatus,The Lungs.In Gray,s Anatomy Of Human Body,20th edition, Philadelphia.USA: Lea & Febiger;2012.p.1093-1100.
10. Barbara young, James s.Lowe,Alan stevens, John w .heath. Respiratory apparatus.In Wheaters functional histology,a text and colour atlas,5th edition,Elsevier;2007.p.234-245.
11. Demos NJ, Teresi A Congenital lung malformations. A unified concept and a case report. J Thorac Cardiovasc Surg 1975; 70:260–264.
12. Heithoff KB, Sane SM, Williams HJ, et al Bronchopulmonary foregut malformations. A unifying etiological concept. AJR 1976;126:46–54.
13. Haller JA, Golladay ES, Pickard LR, et al Surgical management of lung bud anomalies: lobar emphysema, bronchogenic cyst, cystic adenomatoid malformation, and intralobar pulmonary sequestration. Ann Thorac Surg 1979;28:33–43.
14. Keslar P, Newman B, Oh KS. Radiographic manifestations of anomalies of the lung. Radiol Clin North Am 1991; 29:255–270.
15. Evrard V, Ceulemans J, Coosemans W, et al. Congenital parenchymatous malformations of the lung. World J Surg 1999;23:1123–1132.
16. Coran AG, Drongowski R. Congenital cystic disease of the tracheobronchial tree in infants and children. Experience with 44 consecutive cases. Arch Surg. 1994 May;129(5):521-7.
17. Al-Bassam A, Al-Rabeeah A, Al-Nassar S, Al-Mobaireek K, Al-Rawaf A, Banjer H, Al-Mogari I. Congenital cystic disease of the lung in infants and children (experience with 57 cases).Eur J Pediatr Surg 1999 Dec;9(6):364-8.
18. Cangiarella J, Greco MA, Askin F, Perlman E, Goswami S, Jagirdar J.Congenital cystic adenomatoid malformation of the lung: insights into the pathogenesis utilizing quantitative analysis of vascular marker CD34 (QBEND-10) and cell proliferation marker MIB-1. Mod Pathol 1995 Dec;8(9):913-8.
19. Koningsbruggen S, Ahrens F, Brockmann M, Michalk D, Rietschel E. Congenital cystic adenomatoid malformation type 4. Pediatr Pulmonol 2001 Dec;32(6):471-5.
20. Lima M, Gargano T, Ruggeri G, Manuele R, Gentili A, Pilu G, Tani G, Salfi N. Clinical spectrum and management of congenital pulmonary cystic lesions.Pediatr Med Chir. 2008 Mar-Apr;30(2):79-88.
21. Bunduki V, Ruano R, da Silva MM, Miguelez J, Miyadahira S, Maksoud JG, Zugaib M. Prognostic factors associated with congenital cystic adenomatoid malformation of the lung. Prenat Diagn 2000 Jun;20(6):459-64.
22. Priest, Gretchen M. Williams, Ashley Hill, Louis P. Dehner and Adam Jaffe. Pulmonary Cysts in Early Childhood and the Risk of Malignancy.Pediatric Pulmonology 2009;44:14–30.

23. Cass DL, Quinn TM, Yang EY, et al. Increased cell proliferation and decreased apoptosis characterize congenital cystic adenomatoid malformation of the lung. J Pediatr Surg 1998; 33(7):1043-6.
24. Wang NS, Chen MF, Chen FF. The glandular component in congenital cystic adenomatoid malformation of the lung. Respirology 1999 Jun;4(2):147-53.