A report of adenocarcinoma *in situ* and congenital pulmonary airway malformation in a three-day-old infant with a review of the literature

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Association between malignancy and congenital pulmonary airway malformation is a rare entity in childhood. Herein, we describe a three-day-old infant with respiratory distress and cystic lung lesion on her left lung. A lobectomy was performed at the age of three days, and the patient was diagnosed with congenital pulmonary airway malformation and adenocarcinoma in situ.

Key words: congenital pulmonary airway malformation, adenocarcinoma, infant.

Congenital pulmonary airway malformation (CPAM) is a rare developmental abnormality of the lung that has been associated with the presence of rhabdomyosarcoma (RMS), pleuropulmonary blastoma (PBS), and most commonly with bronchioalveolar carcinoma (BAC) and adenocarcinoma of the lung[1-18]. Herein, we describe a three-day-old female infant with CPAM and adenocarcinoma *in situ* (AIS).

Case Report

A full-term female infant weighing 3000 g was born by vaginal delivery at Erciyes University hospital. Prenatally, she had a large lung cyst on her left lung, which pushed the mediastinum and the heart to the right. Her 1-min Apgar score was 3, and she was intubated in the delivery room because of respiratory distress. Chest roentgenogram revealed a space-occupying lesion on her left lung, mediastinal shift to the right, and compression on the right lung fields. Chest computerized tomography (CT) of the patient showed a large multiseptated cystic lesion in the left hemithorax with severe right-sided mediastinal shift, and the patient was considered as having CPAM (Fig. 1). Because of the respiratory distress, mediastinal shift and compression on the right lung, a left upper lobectomy was performed at three days of age. At the age of 13 days, the patient was extubated, and she was discharged home at the age of 25 days.

In the gross examination, the pathological specimens showed multiseptated large cysts. These cysts were lined by pseudostratified ciliated columnar epithelium consistent with CPAM type 1 (Fig. 2a). In some areas, the alveolar spaces were lined with monolayer mucinous cells concomitant with adenocarcinoma (Fig. 2b). These cells were mucicarmine-positive, suggesting the presence of intracytoplasmic mucin (Fig. 2c). Non-neoplastic areas contained a normal alveolar architecture (Fig. 2a, 2b). Tumoral cells showed expression of thyroid transcription factor-1 (TTF-1) (Fig. 2d). The final diagnosis was CPAM type 1 associated with AIS.

Discussion

Adenocarcinoma *in situ* (AIS) (one of the lesions formerly known as BAC) is a localized, small (<3 cm) adenocarcinoma with growth restricted to the neoplastic cells along preexisting alveolar structures (lepidic growth), lacking stromal, vascular or pleural invasion. Papillary or micropapillary patterns and intra-alveolar tumor cells are absent. AIS is subdivided into non-mucinous and mucinous variants. Tumors that meet the criteria for AIS have been classified formerly as BAC according to the strict definition of the 1999 and 2004 World

Health Organization (WHO) classifications[19]. Therefore, in this paper, we discuss BAC and adenocarcinoma cases together.

Congenital pulmonary airway malformation (CPAM) is considered as a hamartomatous lesion and presents mainly in newborns and infants. Stocker[20] divided CPAM into five categories (0-4) based on the site of the defect in the tracheobronchial tree. Types 1 and 4 CPAM in particular are associated with malignancy[20,21]. In a review of the English-language literature, we found 25 cases (including our own) of primary pulmonary adenocarcinoma (including BAC) associated with CPAM (Table I). The median age was 25.5 years (6 months - 77 years). Eleven of them were in the pediatric age group (≤18 years). To the best of our knowledge, our case is the youngest patient to be diagnosed with CPAM and malignancy. The most common symptoms at onset are productive cough, hemoptysis, dyspnea, chest pain, and recurrent infections (Table I). Our case presented with acute respiratory distress in the delivery room. This presentation is the most common mode of presentation during the neonatal period, secondary to the expansion of the cysts and compression of the adjacent structures[22,23]. Of the 25 cases, 13 were males and 10 were females. No gender predilection was seen. No bilateral cases were reported: 17 lesions were on the left (3 in the left upper lobe, 14 in the left lower lobe), 7 lesions were on the right (5 in the right lower lobe, 1 in the right middle lobe and 1 in the right upper lobe), and there was no information for 1 patient. Our patient's lesion was on the left upper lobe. Lower lobe dominancy is seen in the literature.

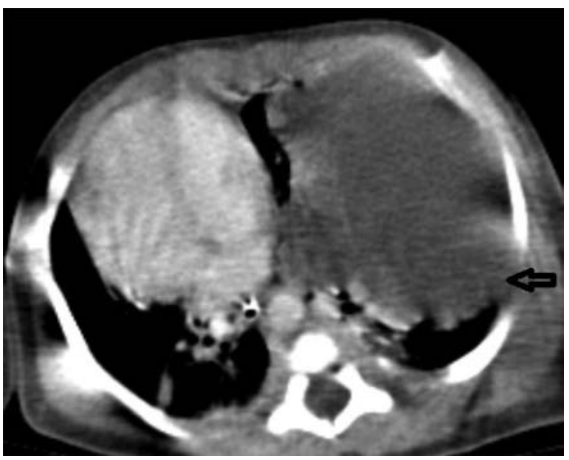

Fig. 1. CT images show a large multiseptated cystic lesion in the left hemithorax with severe right-sided mediastinal shift.

Type 1 CPAMs are reported as showing focal mucous cell hyperplasia in approximately one- third of cases[11], but the incidence of carcinomatous transformation is <1%[6,12]. Sheffield et al.[3] postulated that the observed spread of metaplastic mucous cells from the cyst to the adjacent alveoli might act as a premalignant lesion giving rise to BAC. Moreover, all of the reported cases were associated with type 1 CPAM involving mucous cells, and the malignancies were mucigenic in character; our case was also mucigenic. Preneoplastic alterations in mucogenic- cells include genomic imbalances, increased proliferation, decreased apoptosis, and dysregulated paracrine growth of cells and matrix[3,15].

It is generally accepted that symptomatic lesions should be resected at the time of diagnosis to avoid recurrent infections or respiratory compromise[9]. The treatment of asymptomatic CPAM is defined less clearly. Observation may be a choice, but the patient and/or his family should be informed about both the possibility of infection and the low but definite risk of malignancy. If resection is advised in asymptomatic cases, then most surgeons would schedule surgery between the neonatal period and the first birthday. The lung continues to grow and develop until at least two years of age, and there is some suggestion that there is better catch-up lung growth following early thoracotomy[24].

Adenocarcinoma-associated CPAM occurs at

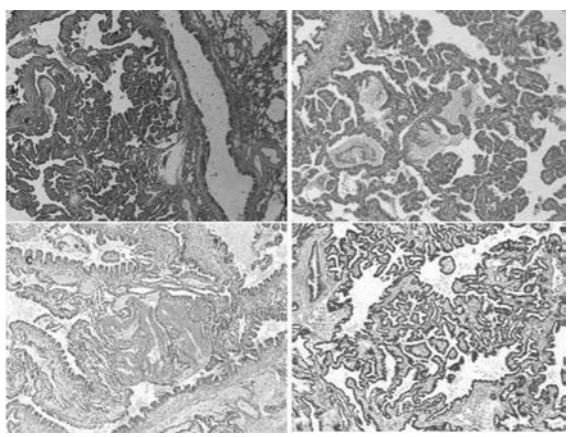

Fig. 2. (a) Alveolar spaces are lined with monolayer cuboidal cells (hematoxylin-eosin (H&E), x100); (b) alveolar spaces are lined with monolayer mucinous cells in some areas (H&E, x100); (c) these cells are mucicarmine-positive (H&E, x200); and (d) immunohistochemical study demonstrates tumoral cells showing expression of thyroid transcription factor-1 (TTF-1) (x200).

Table I. Features of the Cases in the Literature

Reference	Age	Sex	Symptoms	Location	Treatment	Follow-up
1	30	F	Productive cough	LLL	Lobectomy	No information
2	33	F	Productive cough, dyspnea, hemoptysis	RML	Right middle and upper lobectomy	DF, 9 months
3	18	M	Hemoptysis, dyspnea	LUL	Lobectomy	No information
4	19	M	Productive cough	LLL	Pneumonectomy	Died 4 y later
5	20	F	Incidental	LUL	Partial lobectomy	DF after 8 y
5	41	F	Dyspnea	LLL	Lobectomy	DF after 8 y
6	42	F	Incidental	LLL	Lobectomy	DF after 2 y
7	11	F	Chest pain and multiple nodules	RUL	Lobectomy	No information
8	6	M	Pneumonia, cough, chest pain	LLL	Lobectomy	RML metastasis with resection; DF after 7 y
9	11	M	Recurrent pneumonia	LLL	Lobectomy	DF after 1.5 y
10	17	M	Dyspnea on exertion	LLL	Lobectomy	DF after 3 mo
11	6 m	M	No information	RLL	No information	DF after 16 y
	13	M	No information	LLL	No information	DF after 11 y
	18	M	No information	LLL	No information	DF in 2003
	30	F	No information	RLL	No information	DF after 4 y
	36	M	No information	?	No information	No information
12	6	M	Chest pain, cough, hemoptysis, weight loss	LLL	Lobectomy	BAC terminating in invasive AC with metastasis after 15 y
13	60	M	Hemoptysis	RLL	Lobectomy	Mixed AC with BAC pattern
	32	M	Recurrent pneumonia, hemoptysis	LLL	Biopsy of the right lung	Multifocal mucinous BAC
14	8	F	Recurrent pneumonia	LLL	Lobectomy	Metastatic disease after 2 y
15	29	F	Asthma	RLL	No information	No information
16	77	M	Pneumonia	RLL	Lobectomy	DF after 3 y
17	8	F	Chest pain	LLL	Lobectomy	Metastatic disease on right on admission
18	38	M	Hemoptysis	RLL	Lobectomy	No information
Present case	3 d	F	Acute respiratory distress	LUL	Lobectomy	DF after 3 mo

AC: Adenocarcinoma. BAC: Bronchioalveolar carcinoma. DF: Disease-free. F: Female. LLL: Left lower lobe. LUL: Left upper lobe. M: Male. RLL: Right lower lobe. RML: Right middle lobe.

a younger age (median: 25.5 years) when compared with isolated BAC patients (mean age: 59 years)[19]. Carcinoma associated with type 1 CPAM usually occurs in adults whose CPAMs were not resected in childhood[9,12]. These data suggest early resection of CPAM when possible. Iochimescu et al.[12] demonstrated the presence of a continuum of lesions including atypical adenomatous hyperplasia, BAC and invasive adenocarcinoma. The finding of two cases of BAC in asymptomatic patients with CPAM[5,6] and our case show malignant changes in CPAM in the newborn period. These are further suggestions that type 1 CPAM predisposes to the development of adenocarcinoma and needs to be completely resected at the time of detection.

Benjamin et al.[4] described a patient who developed BAC at 19 years of age after resection

of CPAM in infancy. Interestingly, Summers et al.[17] presented a case with metastasis to the opposite side of the lung on admission. Therefore, it is recommended that patients with CPAM, even if resected, should be followed closely for malignancy.

In conclusion, this case of AIS type 1 CPAM occurring in a three-day-old infant highlights the importance of early diagnosis of CPAM and demonstrates that malignant transformation might start in the uterus in type 1 CPAM patients. Furthermore, this case suggests that early resection of CPAM, even if asymptomatic, and close follow-up because of potential malignant degeneration should be recommended.

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