Bronchioloalveolar carcinoma arising in congenital pulmonary airway malformation in a neonate

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Abstract

Congenital pulmonary airway malformation (CPAM), previously known as congenital cystic adenomatoid malformation (CCAM), is a rare developmental lung abnormality with the potential for malignant transformation. Bronchioloalveolar carcinoma (BAC), pleuropulmonary blastoma (PPB), rhabdomyomatous dysplasia/rhabdomyosarcoma (RMS) have been associated with CPAM. We report an unusual case of a 1-day-old male newborn who underwent lobectomy for a cystic lung lesion, which was found to be a mucinous BAC with K-ras mutation in a type 1 CPAM. The case supports the relationship between type 1 CPAM and BAC/KRAS mutant, and highlights that the malignant transformation can occur in very early stage of the infancy.

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ABTRACT:

Congenital pulmonary airway malformation (CPAM), previously known as congenital cystic adenomatoid malformation (CCAM), is a rare developmental lung abnormality with the potential for malignant transformation. Bronchioloalveolar carcinoma (BAC), pleuropulmonary blastoma (PPB), rhabdomyomatous dysplasia/rhabdomyosarcoma (RMS) have been associated with CPAM, but it generally occurs in older children and adults. We report an unusual case of a 1-day-old male newborn who underwent lobectomy for a cystic lung lesion, which was found to be a mucinous BAC with K-ras mutation in a type 1 CPAM.

To the Editor,

A male fetus was diagnosed antenatally with large left CPAM. It was identified at the anomaly scan, and noted to be unusually large with mediastinal shift. **(Figure 1)** This persisted throughout the antenatal period with no regression. He was born by induced vaginal delivery at 38+4 weeks, weighing 3.09kg. He immediately required mechanical respiratory support. Further instability in his respiratory function led to several escalating modalities, including inhaled nitric oxide iNO at 20ppm. He also developed circulatory failure, mixed acidosis and hypotension thus was commenced on adrenaline up to 0.3mcg/kg/min. The Chest X-ray **(figure2A)** showed a large lesion occupying the entire left hemithorax with significantly right-shifted mediastinum. A chest CT **(Figure2B)** confirmed a likely CCAM multicystic lesion with air-fluid levels in LUL. On cardiac echocardiography a small muscular ventricular septal defect was detected. The respiratory and circulatory dysfunction continued to make his condition parlous and surgical treatment was considered to reduce mediastinal shift. Surgery (left upper lobectomy) was performed on day 1 with good post-operative recovery. There was prolonged air leak from chest drain, that was removed after 14 days. His functional lung reserve appeared initially low and he was supported with non-invasive ventilation for a prolonged period to support growth and recovery. He was discharged at 8 weeks of age, supported by nocturnal non-invasive ventilation (CPAP) and NG tube feeding.

Histology confirmed type 1 CPAM (with focal areas of type 2 histology) and highlighted multiple foci of mucinous cells lining the wall of the cysts and focally showing lepidic growth pattern, best regarded as mucinous BAC arising in a CPAM **(figure 3)** , however the lesion was completely resected. Cytogenetic study on DNA extracted from the sample tested by MALDI-TOF mass array spectrometry for 28 activating variants in KRAS identified the KRAS c.35G>A p.(Gly12Asp) variant.

Following the diagnosis, the paediatric oncology team were consulted. Modified staging was undertaken and no evidence of metastatic spread was seen. A repeat CT at six weeks of age showed no contemporaeous lesions in the other lung. The oncology team recommended no further adjunctive therapy and considered the lesions curatively treated. Long term follow up with regular imaging will be required.

Congenital pulmonary airway malformations (CPAM) consist of a spectrum lung malformations affecting different portions of the tracheobronchial tree. The incidence of CPAM is estimated at 1/25000–1/35000 births. CPAM is often diagnosed antenatally by ultrasound, allowing prompt and appropriate medical and surgical management after birth. The natural history and clinical spectrum of CPAM is highly variable. This can range from complete regression antenatally to life-threatening hydrops fetalis. It may present significant cardiorespiratory compromise at birth as seen in our patient. Moreover, the potential for malignant transformation is recognized in CPAM. The most commonly used classification in the pathology literature is the revised Stocker classification[1] who described five types of CPAM (types 0-4) based on cyst size and histology. Stocker proposed changing the name from CCAM to CPAM since the lesions are cystic in only

three of the five types, and adenomatoid in only one type. The distinction between histological subgroups remains important, as some types of cancer are more common in some histologic types of CPAMs. Almost all reported cases in the literature arise in type 1 CPAM. The suggested BAC incidence is approximately 1% of type 1 CPAM [2]. The majority of patients developed BAC in an older age. There are only a few patients under age of 16 with type 1 CPAM who developed BAC, with the reported youngest age being 6 years[3]. Occasional neonatal or infant BAC in CPAM has been reported. Clusters of mucogenic cells are believed to be the precursor cells of mucinous BAC and are described in type 1 CPAM. Mutation of KRAS has been reported in cases of BAC arising in CPAM[4]. However, the molecular mechanism of CPAM malignant transformation is still largely unknown. KRAS mutation occurs most frequently in codon 12 and 13 in exon 1[5], which were observed in the previously reported BAC cases in type 1 CPAM as well as this case. Some authors suggest that malignant transformation in type 1 CPAM may be strongly associated with this mutation[2]. Therefore, the concept of malignant transformation in the sequence from type 1 CPAM to mucous cell hyperplasia to atypical adenomatous hyperplasia to BAC and invasive adenocarcinoma due to K-ras mutation has been proposed. Surgical excision remains controversial in children with practice varying widely between services. It is recognised that excision prevents complications including recurrent infections, pneumothorax and malignancy, in addition to treating the morbidity of CPAM itself, even in asymptomatic cases.

In conclusion, CPAM is a rare congenital pulmonary malformation that may cause respiratory distress in the newborn. Diagnosis by prenatal US allows better parental information, fetal supervision, and detection of associated malformations as well as medical and surgical management immediately after birth, including early surgery. The potential for malignant transformation, usually mucinous BAC, is recognized in type 1 CPAM. The case supports the relationship between type 1 CPAM and lung mucinous BAC/KRAS mutant, and highlights that malignant transformation can occur in very early stage of the infancy in patients with CPAM. In light of these rare cases, the presence of mucinous epithelium in CPAM and completeness of resection should be documented for follow-up purposes.

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