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CASE STUDY

From cystic pulmonary airway malformation, to bronchioloalveolar carcinoma and adenocarcinoma of the lung

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ABSTRACT: Bronchioloalveolar carcinoma (BAC) of the lungs is a known morphological subtype of nonsmall cell cancer. The current study presents several carcinogenetic theories of BAC and the possible relationship with atypical adenomatous hyperplasia and congenital pulmonary airway malformation (CPAM).

The authors present an unusual case of BAC developed in an area of CPAM, with subsequent progression to metastatic adenocarcinoma (AC). The case is unique due to the combination of: early age of presentation; neoplastic transformation of a CPAM; unaltered course over 15 yrs; and its particular pattern of slow morphogenesis and degeneration into an invasive AC of the lung.

The case also presents the unique features of a long-standing, unaltered natural course of paediatric BAC towards invasive and metastatic AC, illustrating that lack of growth over many years cannot be entirely trusted as a criterion of benignity.

In conclusion, clinicians and pathologists need to be aware of the fact that congenital pulmonary airway malformation so far represents the only known pre-invasive lesion for mucinous bronchioloalveolar carcinoma.

KEYWORDS: Adenocarcinoma, atypical adenomatous hyperplasia, bronchioloalveolar carcinoma, carcinogenesis, congenital pulmonary airway malformation, cystic adenomatoid malformation

CASE HISTORY

A 6-yr-old male presented in 1988 with recurrent episodes of fever, left-sided pleuritic chest pain, cough with significant bronchorrhea, intermittent haemoptysis, fatigue, anorexia and weight loss. He was diagnosed with left lower lobe pneumonia and treated with antibiotics three times over a period of 7 months. During the last episode, the chest radiograph showed an infiltrate and air–fluid level in the left lower lobe. He was hospitalised and started on antibiotic therapy. He had a negative tuberculin test, fungal serologies and bronchoalveolar lavage cultures for bacteria, acid-fast bacilli and fungi. A thoracotomy with left-lower lobe lobectomy was performed; macroscopically, the lesion resembled a pneumonic process or a congenital malformation (intra-lobar sequestration with a large secondary abscess *versus* a congenital cystic malformation). Microscopic examination of the resected lung revealed multicentric mucinous-type bronchioloalveolar carcinoma (BAC) developed in an area of congenital adenomatoid malformation (CAM), or congenital pulmonary airway malformation (CPAM) type I, without pleural involvement. No abscesses were found. Synchronous nodules in the right upper, middle, lower and left-lower lobes were present and surgically explored. A right-middle lobe wedge resection biopsy revealed similar lesions of BAC. Chemotherapy was offered, but in light of poor predicted prognosis, the patient's family refused any therapeutic modality.

During the follow-up, the patient had intermittent chest pains, but no other symptoms. He finished school with good grades, smoked cigarettes infrequently and continued to live an active life for the following 15 yrs. Follow-up chest radiographs and computed tomography (CT) imaging were performed on an infrequent basis. The most recent CT scan available for review was from 1988 (fig. 1), which showed stable, nonprogressive, bilateral nodular disease.

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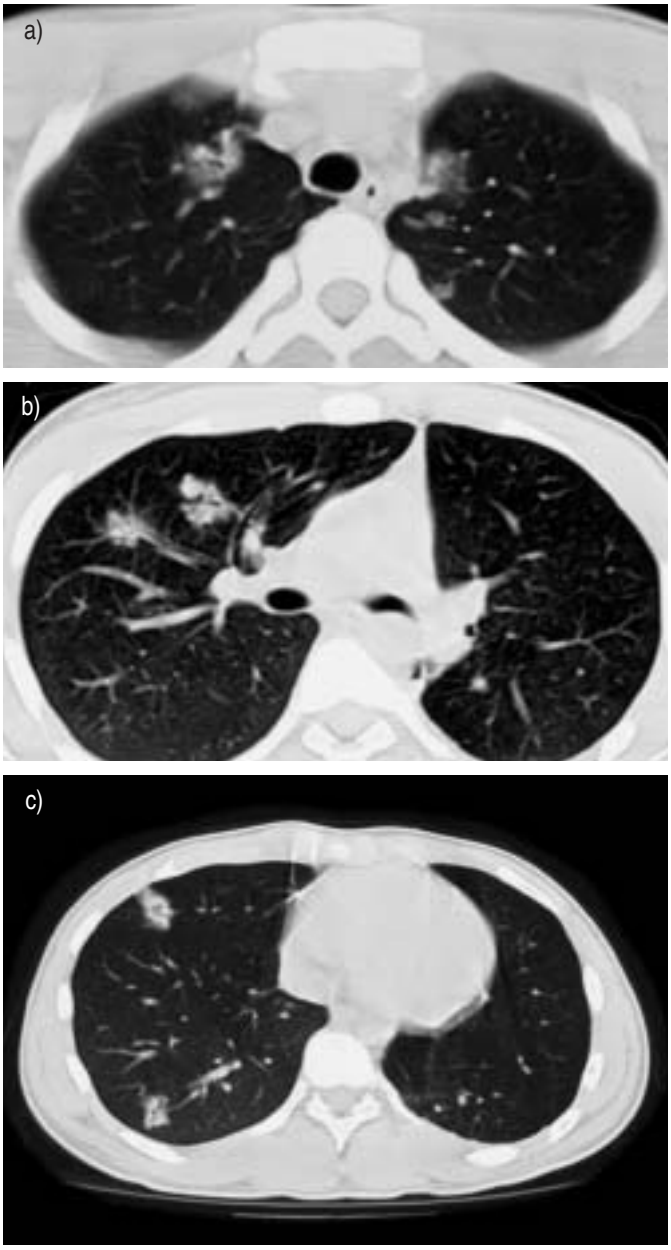

FIGURE 1. Computed tomography scans of the chest obtained in 1988 showing a) right and left upper lobe hazy infiltrates, b) right upper lobe bronchocentric lesions, and c) nodules with minimal (pseudo)cavitation.

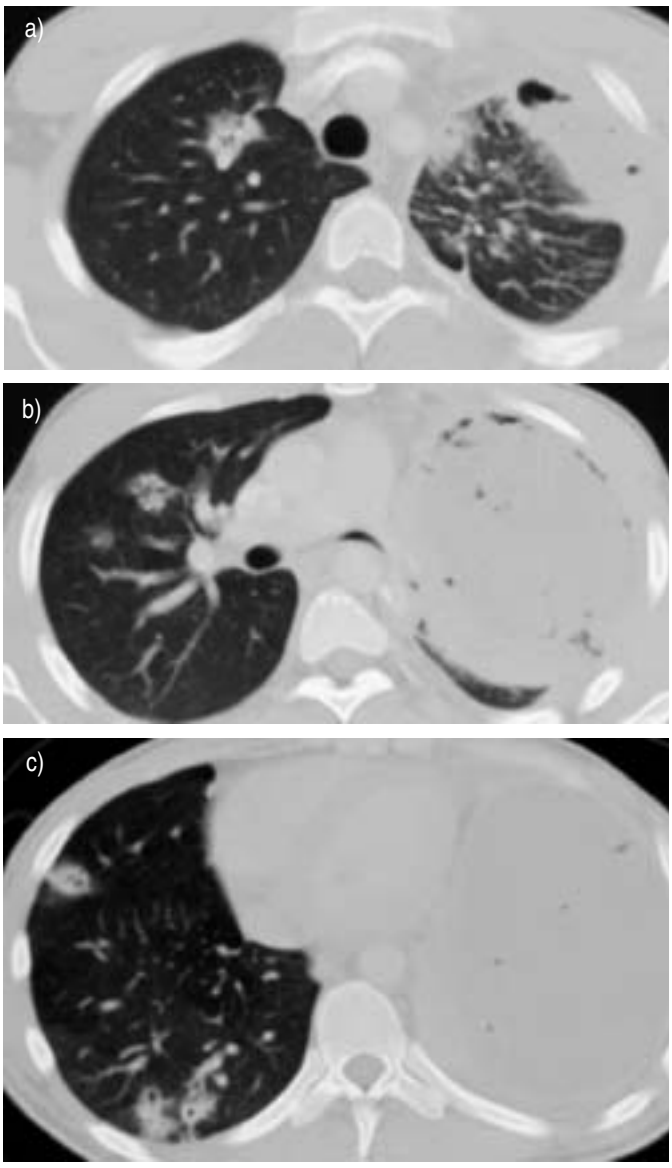

FIGURE 2. Computed tomography scans from 2003 showing a) slightly larger right upper lobe, b) correspondent lesions, and c) new loculated left pleural effusion and more prominent lesions on the right, also with (pseudo)cavitation .

In 2003, aged 21 yrs, the patient was diagnosed with a loculated left-sided pleural effusion, for which he underwent chest tube placement, drainage of a nonpurulent, culture-negative exudative effusion and 2 weeks of *i.v.* antibiotic therapy. One month later, pleural fluid re-accumulated. The chest radiograph and CT scan revealed a loculated left pleural effusion with air–fluid levels and a thick pleural peel. There was no mediastinal, hilar, or axillary lymphadenopathy. There were bilateral pulmonary nodules, and one of the nodules on the right side appeared larger in size, with minimal (pseudo)cavitation (fig. 2).

A thoracentesis, followed by chest tube drainage, revealed an exudative nonchylous pleural fluid with a glucose level of 2 $mg \cdot dL^{-1}$, lactate dehydrogenase of 6,456 $IU \cdot L^{-1}$ and no malignant cells. Video-assisted thoracoscopic biopsy of the right upper and middle lobe nodules was performed, which showed multicentric BAC of mucinous type (fig. 3), and microscopic foci of adenocarcinoma (AC), with invasion of the underlying stroma (fig. 4), which characterises an AC of mixed subtype according to World Health Organization (WHO) classification [1].

The video-assisted thoracoscopic biopsy was compared with biopsies taken in 1988. It appeared that the BAC lesions were similar to the initial neoplastic findings (fig. 5), which arose within a congenital CPAM (fig. 6). Due to persistent drainage, the thick pleural ''peel'' on the CT scan and fluid cultures showing methicillin-sensitive *Staphylococcus epidermidis*, a left pleurectomy, complete with an omental flap closure and

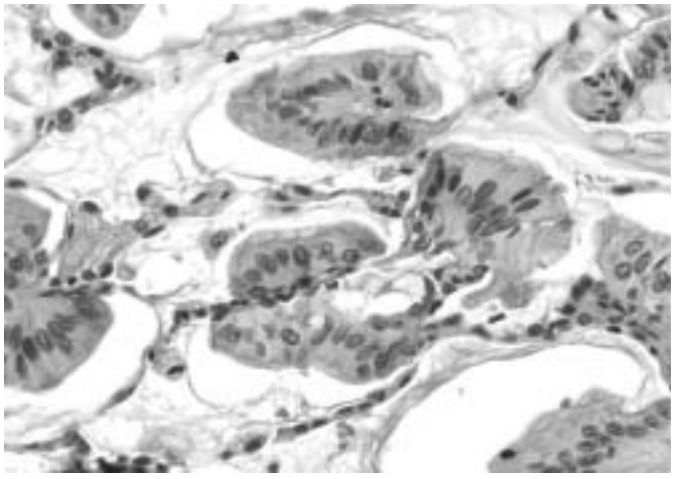

FIGURE 3. Haematoxylin-eosin stain of bronchioloalveolar carcinoma specimen, constituted by columnar atypical cells showing areas of lepidic growth (courtesy of C. Farver).

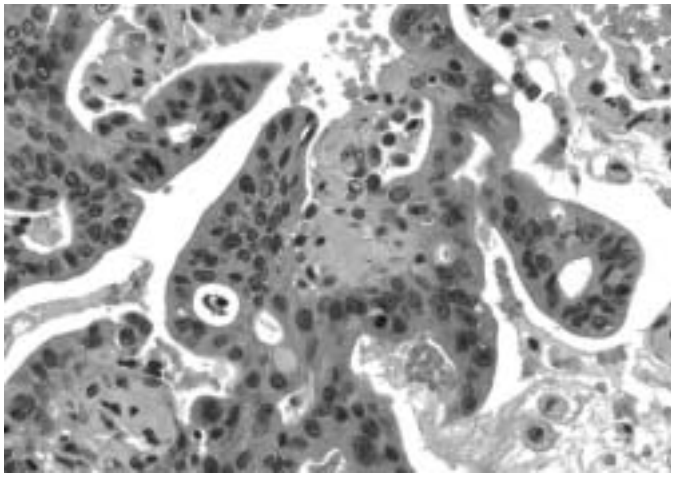

FIGURE 4. Haematoxylin-eosin stain of adenocarcinoma of the lungs showing more cellular atypical and abnormal architecture, with local stromal invasion (courtesy of C. Farver).

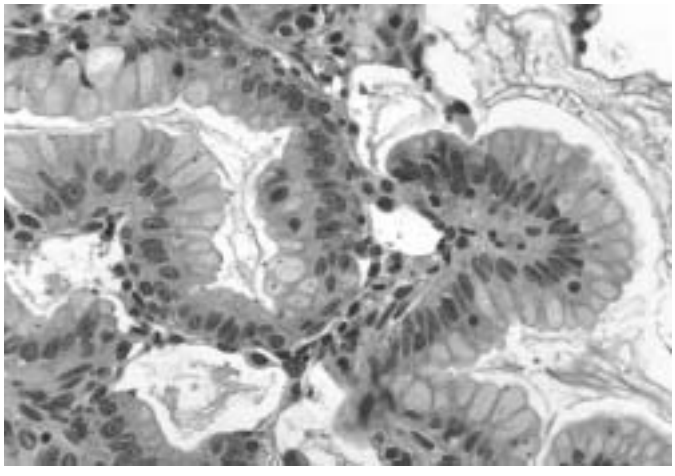

FIGURE 5. Haematoxylin-eosin stain from 1988 of the initial mucinous bronchioloalveolar carcinoma specimen, constituted by columnar atypical cells (courtesy of C. Farver).

diaphragm resuspension, was performed. The pleural biopsy showed metastatic, partially necrotic, mucinous BAC with microscopic foci of well-differentiated AC of mixed type with predominant BAC component.

The patient had an uneventful post-operative recovery, and completed a 4-week course of *i.v.* antibiotic therapy. The patient previously had a nongrowing tumour (in spite of recent progression and evidence of more invasive features), and recognising the uniqueness of the situation, the patient and family together refused any multi-modality therapy. Three months after discharge, the patient developed significant mediastinal lymphadenopathy and multiple metastatic bone lesions. At this time he agreed to enrol in a compassionate therapy programme with single agent gefitinib. He died of metastatic disease 3 months later.

DISCUSSION

Lung cancer is the most frequent cause of cancer death in the USA and worldwide [2]. The WHO classification of lung tumours [1, 3] remains the basis of lung carcinoma nomenclature. Pulmonary AC has become the most frequent histotype (~40%). Unlike the tumourigenesis of squamous cell carcinoma, the precursor lesions and the morphogenesis of lung AC are less clear. Areas of atypical adenomatous hyperplasia (AAH) or CPAM may represent precursor lesions of BAC, while more dysplastic areas may constitute foci of AC. This pattern of morphogenesis could be similar to the progression of colonic benign polyps into atypical dysplastic lesions, and then to AC [4].

Congenital pulmonary malformations are rare when compared with other lung conditions [5]. CPAM [6] or CAM [7, 8] are unusual conditions characterised by immature, malformed lung tissue with cystic appearance (fig. 6), which results from an abnormality of branching morphogenesis of the lungs. There are several CPAM subtypes: 1) 0–3, which arise from the bronchiolar-type epithelium during the pseudoglandular stage of lung development; and 2) type 4, arising from acinar-alveolar type of epithelium, and thought to originate from the saccular stage of development. An imbalance between cellular apoptosis and proliferation during organogenesis could represent the backbone of the transformation which leads to CPAM. An adenomatous overgrowth of terminal bronchioles and alveoli leads ultimately to large masses, which are communicating with the tracheobronchial tree, and have feeding vascularisation from the pulmonary (bronchial) circulation. They can produce multiple intercommunicating cysts lined by cuboidal or pseudostratified, ciliated epithelium and, in about 30% of patients, by mucinous cells [9].

The prenatal diagnosis of CPAM is made by ultrasonography (US) or magnetic resonance imaging (MRI) studies. The postnatal diagnosis is generally made radiographically (chest radiographs or CT scans). CPAM needs to be differentiated from other cystic lung lesions, such as bronchopulmonary sequestration (BPS). In a report in 1999, by CONRAN and STOCKER [10], 50% of the cases of BPS were associated with CPAM. On prenatal US or MRI examination, BPS appears as a well-defined, homogeneous, echodense mass [11]. In contrast, BPS has no connection to the tracheobronchial tree and is supplied by an anomalous systemic artery, rather than the

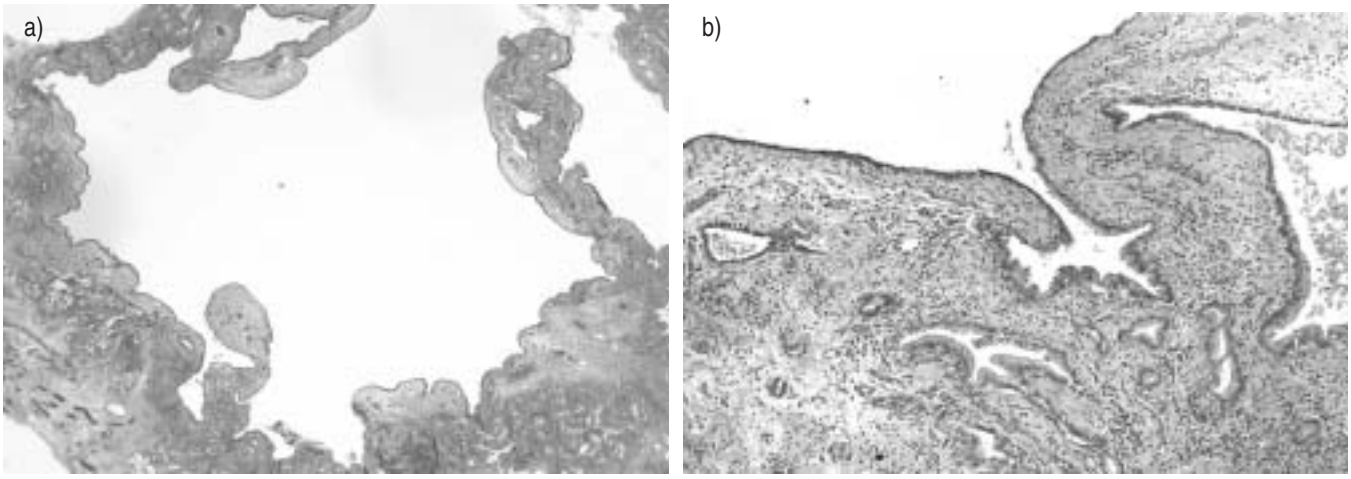

FIGURE 6. Haematoxylin-eosin stain showing areas of cystic airway pulmonary malformation from a biopsy taken in 1988 in a) low and b) high power view.

pulmonary circulation. The artery can be demonstrated by colour flow Doppler study or angiogram, and in 77% of cases derives directly from the aorta [10]. Furthermore, hybrid lesions with characteristics of both CPAM and BPS, and a systemic arterial supply, have been reported [12].

Described initially in 1960 by LIEBOW [13], BAC is considered a distinctive subtype of peripheral AC. Among common lung cancer subtypes, BAC has the lowest association with chronic cigarette smoking. As originally defined, BAC has four major features: 1) distal origin; 2) well-differentiated cytology; 3) growth along intact alveolar septa; and 4) aerogenous or lymphatic spread. The revised WHO classification of lung cancer restricts the definition to tumours without stromal, pleural or lymphatic invasion. To differentiate pulmonary from metastatic AC of other origins (*e.g.* gastrointestinal and genitourinary tracts), the definition mandates exclusion of any history of AC elsewhere. Microscopically, there are three types of BAC: 1) mucinous (rare, presenting with significant bronchorrhea; figs 3 and 5); 2) nonmucinous (the majority); and 3) mixed-type. Mucinous BAC is well differentiated and comprised of goblet cells, which are tall, columnar cells with uniform aspect of the nuclei. However, nonmucinous BAC is formed of single cells, acinar, or papillary clusters, comprised of lepidic growth (single cell row) of Clara or type II alveolar cells lining preserved alveolar walls.

There is still a significant overlap between high-grade AAH and BAC, due to a continuously progressive level of atypia between them, and given their similar clinical courses. Based on these considerations, MILLER [14] suggested that high-grade AAH lesions >5 mm in diameter should be automatically considered BAC, which in fact is not recommended by the 2004 WHO classification [1]. The different morphological patterns and clinical outcomes of the subtypes of BAC suggest differences in their biological behaviour. Previous reports have shown that the mucinous form of BAC is characterised by frequent mutations at codon 12 of the K-ras gene, whereas the other two histotypes show a frequency of K-ras mutations which are no different from those observed in conventional lung AC. More recently, it was shown that in fact <15% of AC have K-ras mutations [15]. Loss of heterozygosity at microsatellite-containing loci located within the fragile histidine triad (FHIT) gene was observed in 43% of BACs [16]. The distribution of FHIT gene abnormalities was not statistically different in the three histological subtypes. Conversely, p53 mutations were present in 32% of nonmucinous/sclerosing BACs, while no p53 mutations were seen in mucinous tumours. Correlations with clinicopathological parameters showed that p53 mutations in BACs are associated with more aggressive tumours. No correlations were observed between FHIT or K-ras gene abnormalities and clinicopathological data.

BAC is one of the subtypes of AC that has been separated due to its excellent survival when <2 cm in diameter at the time of diagnosis, *i.e.* almost 100% 5-yr survival [17].

AC represents up to 40% of primary pulmonary tumours, and is a neoplasia that is less strongly associated with smoking. It is often a parenchymal peripheral lesion, occasionally involving the pleura, with or without an associated pleural effusion. The theory that peripheral AC may arise in areas of scarring (''scar carcinoma''), such as those seen in old, healed tuberculosis or other similar lesions, is currently out of favour [18]. Some investigators even suggest that the scar formation is actually due to the carcinoma in areas where lung fibrotic and neoplastic lesions coexist [19].

Histologically, tumours are graded as well, moderately or poorly differentiated, with the majority showing moderate differentiation. The degree of differentiation can be very heterogenous topographically, with areas of well-differentiated cells alternating with more atypical cell islets (fig. 6). ACs are diagnosed according to five major subtypes (mixed, acinar, papillary, bronchioloalveolar and solid) and several rare variants (clear cell, signet-ring cell, foetal type, colloid and cystadenocarcinoma) [1]. Due to frequent heterogeneity, most diagnoses are of mixed type AC (85%). Special stains such as periodic acid Schiff or mucicarmin may be needed to demonstrate intracellular mucin. The cells of AC are often more uniform than those of epidermoid carcinoma or large cell carcinoma. They are usually large, with big nuclei, high nuclear–cytoplasmatic ratio and prominent eosinophilic

nucleoli. The cytoplasm may appear vacuolated due to mucin production. Unlike squamous cell carcinoma, the cytoplasmic borders are often blurred or indistinct. AC cells can also present unusual patterns, *i.e.* clear-cell, signet or ring cell. Spindle-cell features now belong to sarcomatoid carcinomas. In general, the AC cells are more uniform than those of squamous cell carcinoma or large cell carcinoma.

The immunohistochemical stains are not usually necessary to diagnose AC, although they may be useful in differentiating it from metastatic tumours or from mesothelioma [20]. The latter differentiation can be challenging on cytological specimens and frequently requires additional studies. The pleural involvement by AC, which is very important in tumour staging, may need documentation with elastic stains. AC is often associated with mucin production, and in poorly differentiated tumours, special stains may be needed to detect mucin. This feature may be useful in distinguishing lesions of AC from otherwise identical-appearing large cell carcinoma.

The missing links

Morphogenesis of the lung, which includes differentiation from the primitive foregut, development of the airways by branching morphogenesis and maturation of the parenchymal cells with production of lung-specific proteins, is recapitulated (at least in part) during lung malformation and carcinogenesis. Different growth factors, transcription regulators and various oncogenes seem to interact at multiple dichotomy points, with a subsequent vast array of morphotypes.

There is good morphological evidence that low-grade AAH may progress to high-grade AAH, then to BAC (which is by definition a noninvasive lesion), and then to a peripheral lung AC. This theory stems from astute clinical observations, morphometric, immunohistochemical and other molecular biology studies. Over the years, morphological data has shown how difficult it is to differentiate high-grade AAH from BAC, the fact that cystic AAH lesions could mimic CPAM of the lungs, and that sometimes areas of well-defined BAC are surrounded by lesions of AAH. There were studies that looked specifically for areas of AAH in necrotic lungs and found a significantly low incidence of AAH (2%) [21], lower than the data from resected lungs for primary pulmonary malignancy (23–34% of lungs resected for AC) [22–24]. It is worth noting that, given the small size of the lesions, the sampling error also underestimates the real incidence of AAH lesions. Several authors reported patients with multiple synchronous AAH lesions; interestingly, almost all of them also had areas of BAC or primary lung AC. In a study of 70 patients with AAH (between six and eight AAH lesions, n=8; between 12 and 42 lesions, n=4), all patients had foci of AC. Of the 70 patients, 10 had multiple synchronous AC (up to six pieces per resected specimen) [24]. Clinical associations have been described between AAH and Li-Fraumeni syndrome [25], or tuberous sclerosis [26], which suggested that multiple AAH/AC lesions could arise in patients with certain genetic predisposition.

There are scattered reports relating the occurrence of CPAM with malignant conditions, *i.e.* rhabdomyosarcoma in children [27–30] and mucinous BAC (mostly in adults) [31–40]. These associations have been significantly underappreciated and it is unlikely that they represent random associations or publication bias. In adults BAC represented 15–20% of all lung cancers, increasing steadily since the 1980s [41, 42]. The mean age at the time of diagnosis is 59 yrs. According to the new definition, BAC does not exceed 3% of lung cancers. Cases of BAC developed within areas of CPAM have a mean age of 26 yrs, and all have mucinous character [43]. The current authors believe that there is enough data to support the theory of CPAM transformation and subsequent development of BAC through the migration of the mucinous, metaplastic cells along the alveolar septae from the cysts to the adjacent parenchyma, and then to mixed-type AC. Since CPAM poses significant risks of malignant transformation or superinfection, many advocate surgical resection, even in asymptomatic patients [43].

In conclusion, this case illustrates a well-documented transformation of a congenital pulmonary airway malformation into a mucinous-type bronchioloalveolar carcinoma, and subsequently into an adenocarcinoma of mixed type with bronchoalveolar elements. The clinicians and pathologists need to be aware of the fact that while atypical adenomatous hyperplasia may be a precursor lesion of type II Clara cell, nonmucinous bronchioloalveolar carcinoma, congenital pulmonary airway manifestation so far represents the only known pre-invasive lesion for mucinous bronchioloalveolar carcinoma. The present case also illustrates the unique feature of a long-standing, unaltered natural course of a paediatric bronchioloalveolar carcinoma towards invasive and metastatic adenocarcinoma, which points out that lack of growth over many years cannot be entirely trusted as a criterion of benignity.

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