Malignancies in congenital cystic adenomatoid malformations (CCAMs) of the lung are rare. We report a 41-year-old male patient with a pulmonary cystic lesion suspicious for CCAM, unrecognized until the patient was 40 years of age, and which subsequently became more consolidated during the interval between initial presentation and surgery. Microscopic examination of the resected specimen revealed features of type 1 CCAM with a mucinous adenocarcinoma, metastatic to the mediastinal lymph nodes. This case illustrates the importance of prompt surgical resection for all suspected CCAMs, especially those discovered in adulthood.

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Adenocarcinoma in Adult CCAM

imen had a relatively solid area (70%) with poorly preserved hemorrhagic cystic spaces (Fig. 3). Cystic changes were found in the periphery of the lobe. Histologically, the cysts were lined by pseudostratified ciliated columnar cells with underlying fibrous tissue and smooth muscle, but scant cartilage. This was consistent with a type 1 CCAM, based on Stocker’s classification (Fig. 4A). The bulk of the lesion consisted of tall columnar mucosecretory epithelial cells in bronchioloalveolar and solid patterns, with mucin production, consistent with adenocarcinoma, mixed subtype (Fig. 4B, C). Although the transition from bland columnar epithelial cells to atypical cells was indiscernible, the cysts adjacent to the typical CCAM demonstrated adenocarcinoma involvement (Fig. 4D). Tumor cells were positive for thyroid transcription factor-1 (TTF-1) and cytokeratin 7 (CK7), but negative for cytokeratin 20 (CK20). However, patients with gastric adenocarcinoma have a TTF-1 negative, CK7 negative, and CK20 negative immunophenotype (Fig. 5). The mediastinal lymph nodes showed extensive metastasis. The patient was discharged from the hospital after an uneventful post-operative course, and he has been on chemotherapy with no recurrence during one year of follow-up.

Fig. 1. Coronal reconstruction images of the initial chest CT scans demonstrate air-cysts with internal fluid in the right lower lobe, suggestive of an adult form of CCAM with inflammation (A). Seventeen months after the initial scan, the lesion was increased in size and virtually replaced by fluid and consolidation (B).

Fig. 2. Gastric biopsy reveals poorly differentiated tubular adenocarcinoma in the mucosa.

Fig. 3. Gross photograph shows a large well-circumscribed lesion, composed of hemorrhagic spaces and tan white solid glistening components.
Fig. 4. The cysts are lined by ciliated pseudostratified columnar epithelium with underlying fibrous tissue and smooth muscle, consistent with type 1 CCAM. Notice the interspersed goblet cells (A). The solid area reveals mucinous bronchioloalveolar carcinoma (B) and adenocarcinoma with mucin production (C). Malignancy (*) is noted adjacent to the CCAM cysts (**) (D).

Fig. 5. On immunohistochemical staining, the gastric cancer is TTF-1(-)/CK7(-)/CK20(-) (A), while the lung carcinoma is TTF-1(+)/CK7(+)/CK20(-) (B).
CCAM is characterized by anomalous fetal development of the small airways and distal lung parenchyma, which leads to an adenomatoid proliferation of terminal respiratory structures and cyst formation. Most CCAMs are diagnosed and managed within the first two years of life. In rare instances, however, such lesions may remain unrecognized until adulthood. Although frequently complicated by recurrent infection, adult CCAMs may be asymptomatic. Hence, they may be detected only incidentally on routine chest radiography or during a study of a non-pulmonary lesion, as in the present case. Our patient had sought medical attention for his copious sputum. However, he had never undergone a radiologic examination until he suffered ribs fractured in a traffic accident.

A few patients with (or history of) CCAMs have developed carcinomas, usually mucinous BACs. This has led to the suspicion of the potential for malignant transformation in CCAMs. Our case demonstrated mucinous BAC, invasive carcinoma, and features of a type 1 CCAM in the residual cysts. Along with these histological features, the sequential progression of imaging abnormalities provides evidence for tumor development in the setting of CCAM. Mani et al. documented a type 1 CCAM with a full spectrum of precursor (atypical adenomatous hyperplasia) and neoplastic lesions (BAC and invasive adenocarcinoma), suggesting the predisposition of type 1 CCAMs toward malignancy. Lantuejoul et al. recently noted loss of heterozygosity on analysis of microsatellite alterations and direct sequencing polymerase chain reaction for molecular studies in seven cases of type 1 CCAM with associated mucinous proliferation. The mucinous cells were found to share the same differentiation profile with the corresponding mucinous BAC cells, thus justifying their consideration as BAC precursors. An earlier study of 22 CCAMs also revealed gains in chromosomes 2 and 4 in both atypical goblet cell hyperplasia and carcinoma, but not in respiratory-type surface epithelium or surrounding normal lung tissue. This supports the pre-neoplastic status of goblet cell proliferation in CCAM.

All 16 cases of type 1 CCAM-related malignancies previously reported in the medical literature were BACs, exclusively mucinous type, with or without invasive carcinoma (5 including the present case vs. 12). Most patients (11/17, 65%) were adults. Of the five children with available follow-up, one died of disease at 15 years of age, and four were free of disease for a period ranging from 18 months to 16 years. Of the six adult patients with available follow-up, one died of disease at 4 years, and five were free of disease for 3 months to 4 years. There are too few such cases to characterize the differences in prognosis between pediatric and adult patients. However, the age at diagnosis ranged from 6 months to 60 years, with a mean age of 25.2 years, which is much younger compared to the mean age of BAC diagnosis in the general population (59 years). This supports the fact that carcinoma associated with type 1 CCAM usually occurs in adults whose CCAMs have not been resected in childhood. We reported a case of type 1 CCAM that eventually developed metastatic adenocarcinoma during the surgical delay, in order to emphasize the importance of prompt surgical treatment for adult CCAMs. These lesions should be resected as soon as possible to prevent malignant change and progression to invasion.

REFERENCES
