EGFR Mutation of Adenocarcinoma in Congenital Cystic Adenomatoid Malformation/Congenital Pulmonary Airway Malformation: A Case Report

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Received August 7, 2013; accepted December 16, 2013

An 80-year-old man underwent right upper lobectomy for the resection of multiple cysts accompanied by a nodule. The pathological diagnosis was adenocarcinoma with surrounding atypical epithelial cell proliferation in a Type 1 congenital cystic adenomatoid malformation/congenital pulmonary airway malformation. There was epidermal growth factor receptor mutation in the adenocarcinoma and surrounding atypical epithelial cells that had proliferated. Malignant transformation of congenital cystic adenomatoid malformation/congenital pulmonary airway malformation may be related to the epidermal growth factor receptor pathway in this case, with atypical epithelial cell proliferation as a precursor. We emphasize the importance of complete resection of congenital cystic adenomatoid malformation/congenital pulmonary airway malformation and the possibility of treatment with epidermal growth factor receptor tyrosine kinase inhibitors in epidermal growth factor receptor-mutated cases.

Key words: lung cancer – EGFR genes – congenital cystic adenomatoid malformation

INTRODUCTION

Congenital cystic adenomatoid malformation (CCAM)/congenital pulmonary airway malformation (CPAM) is a rare, non-hereditary, maldeveloped lesion of the pulmonary parenchyma characterized by disorganized overgrowth of terminal respiratory structures, resulting in cysts of various sizes in the lung. In children, surgical resection is recommended due to the high probabilities of infection, pneumothorax and development of malignancies. However, the etiology and management of this disease remain unclear and controversial. In recent years, genetic profiles such as positive mutation status of the K-ras gene of malignant lesions in CCAM/CPAM have been described, which justifies the consideration of CCAM/CPAM as a premalignant lesion. To the best of our knowledge, this is the first case report of epidermal growth factor receptor (EGFR)-mutated adenocarcinoma arising in CCAM/CPAM.

CASE REPORT

An 80-year-old man was referred to our institution for surgical resection of multiple cysts with a nodule abutting the cyst wall in the right upper lung lobe. He was a current smoker with a Brinkman index of 650, and was exposed to dust pollution as part of his work history. Multiple cystic lesions in the right upper lobe were incidentally discovered on chest computed...
tomography (CT) 6 years earlier (Fig. 1a); therefore, he was followed by annual CT. A small nodule abutting the cyst wall appeared 1 year earlier. The nodule had enlarged to 18 mm on chest CT performed just before the patient came to our institution (Fig. 1b). On admission, he was asymptomatic without any findings on physical examination, and all of his laboratory tests were normal. Chest CT revealed multiple cysts with a thin wall in the right upper lung lobe. The largest cyst was 45 mm in diameter, and an 18-mm nodule was detected abutting the cyst wall. Right upper lobectomy and hilomedial lymphadenectomy were performed after an intraoperative rapid diagnosis of the nodule as adenocarcinoma. Gross examination of the surgical specimen of the right upper lobe showed 52 × 30 mm multiple cystic lesions replacing lung parenchyma (Fig. 2a) with a 38 × 8 × 37 mm tumor in S2. The pathological diagnosis of the nodule was invasive adenocarcinoma (papillary predominant adenocarcinoma) (Fig. 2b and c). Most of the cysts were lined by a monolayer of atypical epithelial cells; however, some cysts were lined by non-ciliated and ciliated columnar epithelium without atypia (Fig. 2c). The walls of the cysts lined by epithelium without atypia contained a layer of smooth muscle cells, but they lacked cartilage. These findings were compatible with the pathological findings of Type 1 CCAM/CPAM. The microscopic diagnosis of the nodule was invasive adenocarcinoma (papillary predominant adenocarcinoma). Papillary dominant adenocarcinoma was observed adjacent to atypical epithelial cell proliferation in CCAM/CPAM (Fig. 2b). The pathological findings of atypical epithelial cell proliferation resembled those of high-grade atypical adenomatous hyperplasia (AAH) or adenocarcinoma in situ [formerly non-mucinous bronchioloalveolar adenocarcinoma (BAC)]. The papillary predominant adenocarcinoma and atypical epithelial cell proliferative lesions expressed Thyroid transcription factor 1 (TTF-1), Napsin A and carcinoembryonic antigen (CEA). The papillary predominant adenocarcinoma was strongly positive for p53; however, only solitary positive cells were observed in the atypical epithelial cells. The CCAM/CPAM lesion without atypia expressed TTF-1 and Napsin A, but did not express CEA and p53. The papillary predominant adenocarcinoma cells, the atypical epithelial cells and the CCAM/CPAM lesion without atypia were separately dissected from 10-μm-thick specimens, and DNA was extracted for EGFR and K-ras mutational analysis. Mutations in exons 18–21 of EGFR were analyzed, and an L858R point mutation in exon 21 was detected in both the papillary predominant adenocarcinoma and surrounding atypical epithelial cells, but not in the CCAM/CPAM lesion without atypia. There was no K-ras mutation in any of the lesions. The pathological stage was T2aN0M0. The patient was discharged on the sixth postoperative day.

**DISCUSSION**

CCAM/CPAM is a rare, non-hereditary, maldeveloped lesion of the pulmonary parenchyma characterized by disorganized overgrowth of terminal respiratory structures, resulting in cysts of various sizes in the lung. Most CCAM/CPAM patients present early in life, but a few adult cases have been reported. CCAM/CPAM is classified into five types based on gross and microscopic appearance. Type 1 CCAM/CPAM is the most common, accounting for over half of the cases. These lesions are composed of large multilocular cysts ranging from 3 to 10 cm in diameter. Their microscopic appearance is described as cysts with fibrous septa lacking cartilage, lined by pseudostatified, ciliated columnar or cuboidal cells. In recent years, Type 1 CCAM/CPAM has been described as a premalignant lesion. Since adult patients are extremely rare, pulmonary physicians are usually unfamiliar with CCAM/CPAM. Furthermore, other cystic lung diseases such as bullae, bronchogenic cysts or intralobar sequestrations might be difficult to differentiate from CCAM/CPAM based exclusively on

![Figure 1](https://academic.oup.com/jjco/article-abstract/44/3/279/843299)
radiological examination. It is important that CCAM/CPAM be included in the differential diagnosis of cystic lesions in the lung, even in adults.

EGFR is a tyrosine kinase receptor involved in the carcinogenesis of non-small cell lung cancer, mainly adenocarcinomas (1). Most non-mucinous adenocarcinomas with lepidic growth (formerly non-mucinous BACs) have EGFR mutations, whereas invasive mucinous adenocarcinomas (formerly mucinous BACs) are significantly associated with K-ras mutations (2). Type 1 CCAM/CPAM shows malignant transformation usually to invasive mucinous adenocarcinoma (3–5). Type 1 CCAM/CPAM is reported to demonstrate foci of AAH in approximately 10% and atypical goblet cell hyperplasia (AGCH) in 33% of cases. Stacher et al. (6) reported that surface epithelium in Type 1 CCAM/CPAM did not demonstrate chromosomal aberrations; however, these aberrations were present both in adenocarcinoma and in foci of AAH or AGCH detected in CCAM/CPAM lesions. Based on these findings, they concluded that AAH and AGCH may be precursor lesions. Lanteuejoul et al. (7) reported the genetic profiles of mucinous proliferation and corresponding invasive mucinous adenocarcinoma in Type 1 CCAM/CPAM. They both showed K-ras mutations, which suggested the similarity of K-ras genomic profiles between mucinous proliferation and invasive mucinous adenocarcinoma. The authors concluded that mucinous proliferation was very likely a precursor lesion of adenocarcinoma.

To the best of our knowledge, 28 cases of Type 1 CCAM/CPAM with AAH or adenocarcinoma have been reported. Two cases had AAH, 2 cases had mixed mucinous and non-mucinous adenocarcinomas, and 24 cases had mucinous adenocarcinoma. Although cases of malignant transformation of Type 1 CCAM/CPAM to mucinous adenocarcinoma have been frequently reported, the present case had non-mucinous adenocarcinoma with atypical epithelial cell proliferation arising in a Type 1 CCAM/CPAM lesion. Furthermore, in the present case, the same EGFR mutation was detected in both the papillary predominant adenocarcinoma and the surrounding atypical epithelial cells in Type 1 CCAM/CPAM, but not in the CCAM/CPAM lesion without atypia. In contrast, K-ras mutation was negative in all lesions, unlike in previous reports. This supports the hypothesis that the EGFR pathway
caused, or at least participated in, the malignant transformation of CCAM/CPAM. Epithelial cells in CCAM/CPAM may initially transform to atypical epithelial cells via the EGFR pathway. This can be recognized as a preinvasive lesion. Malignant progression to papillary predominant adenocarcinoma then occurs in the second step, which may depend on another pathway. This hypothesis emphasizes the importance of complete surgical resection of Type 1 CCAM/CPAM, since the atypical epithelial cells along the preexisting cyst wall could not be detected on CT and were only able to be confirmed by pathological examination of the resected tissue. Furthermore, it is possible that adenocarcinoma arising in Type 1 CCAM/CPAM can be treated with EGFR tyrosine kinase inhibitors in EGFR-mutated cases. Further studies should address whether EGFR mutation is related to carcinogenesis of Type 1 CCAM/CPAM.

Conflict of interest statement
None declared.

References