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Case Report

Mucinous bronchioloalveolar carcinoma with K-*ras* mutation arising in type 1 congenital cystic adenomatoid malformation: a case report with review of the literature

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Abstract: Congenital cystic adenomatoid malformation (CCAM) of the lung is a rare hamartomatous cystic lesion, characterized by the presence of large cysts, which are histopathologically lined by pseudostratified ciliated cells. It has been recognized that rare cases of type 1 CCAM show malignant transformation, usually bronchioloalveolar carcinoma (BAC) or adenocarcinoma. Herein, we describe a case of BAC arising in type 1 CCAM with K-*ras* mutation. A 9-year-old Japanese girl presented with fever. Computed tomography demonstrated large cystic lesions in her right lower lung. Histopathological study of the resected specimen revealed multiple cysts, which were lined by pseudostratified ciliated cells, and occasionally interspersed with mucous cells without atypia. A small focus of proliferation of columnar cells showing lepidic growth pattern was present. These columnar cells had abundant mucin in the cytoplasm and mildly to moderately enlarged nuclei. Accordingly, a diagnosis of BAC arising in type 1 CCAM was made. Polymerase chain reaction analysis revealed K-*ras* mutation at codon 12 in the BAC component. The presence of mucous cell/goblet cell hyperplasia and atypical adenomatous hyperplasia is a well known phenomenon in type 1 CCAM. A recent study clearly demonstrated K-*ras* mutation in these lesions, which are thought to be precursors of BAC. Therefore, the concept of malignant transformation in the sequence from type 1 CCAM to mucous cell hyperplasia to atypical adenomatous hyperplasia to BAC and invasive adenocarcinoma due to K-*ras* mutation has been proposed. Careful histopathological analysis is important for evaluation of malignant lesions in type 1 CCAM.

Keywords: Congenital cystic adenomatoid malformation, mucinous bronchioloalveolar carcinoma, K-*ras* mutation

Introduction

Congenital cystic adenomatoid malformation (CCAM) of the lung is a rare hamartomatous cystic lesion, and the reported incidence is between 1/25,000 and 1/35,000 [1]. Stocker classified this disorder into five subtypes: namely type 0, 1, 2, 3, and 4 [2, 3]. It has been hypothesized that during the development of this disorder from type 0 to type 4 the abnormalities involve progressively more distal tissue, with type 0 characterized by complete agenesis of acini and type 4 representing cystic change in the peripheral acini, and type 1, 2, and 3 reflect intermediate stages [2-4]. Type 1 is the most common subtype of CCAM, accounting for approximately 60-70% of all cases, and is characterized by the presence of large cysts (up to 10 cm), which are histopathologically lined by pseudostratified ciliated cells that are often interspersed with rows of mucous cells [3, 4].

It has been recognized that rare cases of type 1 CCAM show malignant transformation, usually bronchioloalveolar carcinoma (BAC) or adenocarcinoma [4-16], and the occurrence of rhabdomyosarcoma or pleuropulmonary blastoma has also been rarely documented [17, 18]. Moreover, a recent study clearly demonstrated that the occurrence of BAC in type 1 CCAM is associated with K-*ras* mutation [6]. Herein, we describe the fourth documented case of mucinous BAC with K-*ras* mutation in type 1 CCAM

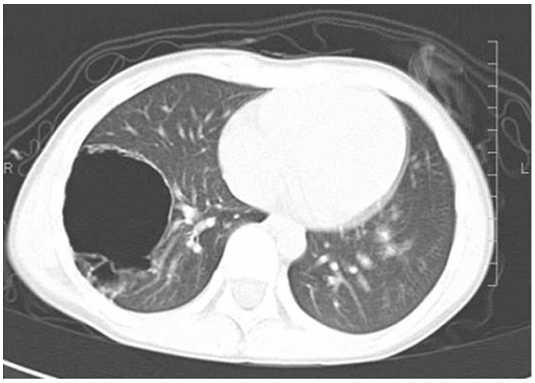

Figure 1. Contrast-enhanced computed tomography showing multiple cystic lesions in the right lower lung. The size of the largest one is 6 x 5 cm in diameter.

and review the histogenesis and clinicopathological features of mucinous BAC in type 1 CCAM.

Case report

A 9-year-old Japanese girl, who had a past history of pulmonary abscess at the age of 6, presented with a fever at an outpatient clinic. Under a clinical diagnosis of pulmonary abscess, antibiotics were administered, resulting in abatement of the fever. Computed tomography demonstrated large cystic lesions in her right lower lung (S8) (**Figure 1**), thus, she was referred to our hospital for operation of the cystic lesions of the lung.

Histopathological study of the resected lung specimen revealed multiple cysts. The largest cyst was 6 x 5 cm in diameter, and the average size ranged from 3 to 5 mm in diameter (**Figure 2A**, **2B**). These cysts were lined by pseudostratified ciliated cells without atypia (**Figure 2B**, inset), and some cysts were interspersed with mucous cells with bland oval nuclei containing small nucleolus (**Figure 2C**). Neither cartilage nor smooth muscle was present around the cysts. These histopathological features were typical for type 1 CCAM.

A small focus of proliferation of columnar cells showing lepidic growth pattern, measuring 1 x 1 mm in diameter, was present under the dilated cyst (**Figure 2D**). These columnar cells had abundant mucin in the cytoplasm and mildly to moderately enlarged round nuclei containing small nucleoli (**Figure 2E**). No invasive growth was noted.

Immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [19-22]. MUC-5AC was expressed in the proliferative columnar cells (**Figure 3**), and MUC6 was focally expressed. However, MUC2 and cdx-2 were not expressed. $p16^{INK4}$ was expressed in the columnar cells (**Figure 3**), but overexpression of p53 protein was not observed. Moreover, TTF-1 was negative.

According to these results, an ultimate diagnosis of mucinous BAC arising in type 1 CCAM was made.

Analysis by polymerase chain reaction-sequence specific primer method for mutation in the K-ras gene revealed that the normal DNA sequence GGT (glycine) at codon 12 was altered to GAT (aspartic acid) in BAC component.

Discussion

In this report, we described the fourth documented case of mucinous BAC with *K-ras* mutation in type 1 CCAM. Since the first description in 1953, it has been recognized that BAC can occur in association with type 1 CCAM [23], and the suggested incidence is approximately 1% of type 1 CCAM [4-16]. Less than 25 cases of BAC arising in type 1 CCAM have been reported in the English literature [4-16]. However, these cases included invasive mixed adenocarcinoma by the 2004 World Health Organization Classification because some of these cases showed lymph node metastases and died of disease [5]. This may have been due to the diagnostic criteria of BAC, which included invasive adenocarcinomas before 2004, but the 2004 World Health Organization Classification restricts the diagnosis of BAC to well differentiated adenocarcinoma without stromal, vascular, and pleural invasion. This disorder affects infant (6 months) to middle-aged persons [4-16]. The main complaints are recurrent pneumonia, cough, or hemoptysis [5, 24]. The left lower lobe is mainly affected, but the right lower lobe can also be involved [5, 24]. Moreover, all reported cases of CCAM-associated BAC have arisen in patients with type 1, and the occurrence of BAC in other types of CCAM have not been described [5].

The presence of mucous cell/goblet cell hyperplasia and atypical adenomatous hyperplasia

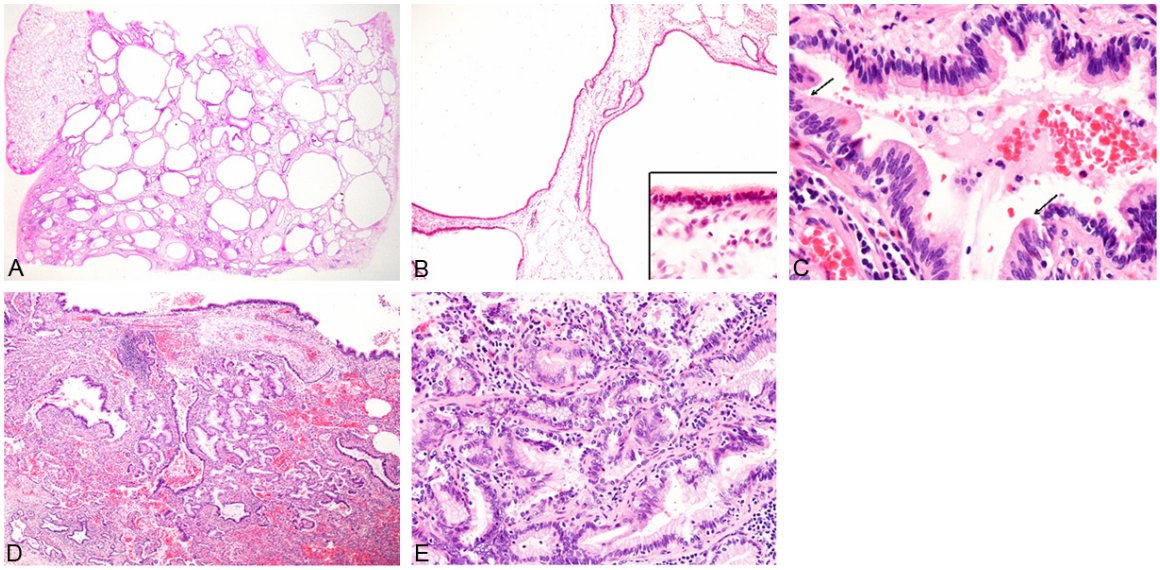

Figure 2. Histopathological features. A: Panoramic view demonstrating multiple cysts ranging from 3 to 5 mm in diameter. HE. B: The cysts are lined by pseudostratified ciliated epithelium (inset). HE, x 40, x 400 (inset). C: The cyst is focally covered by mucous cells without atypia (arrows). HE, x 200. D: A small focus of proliferation of mucous cells showing lepidic growth under a dilated cyst. HE, x 40. E: The proliferative mucous cells have mildly to moderately enlarged round nuclei containing small nucleoli. HE, x 200.

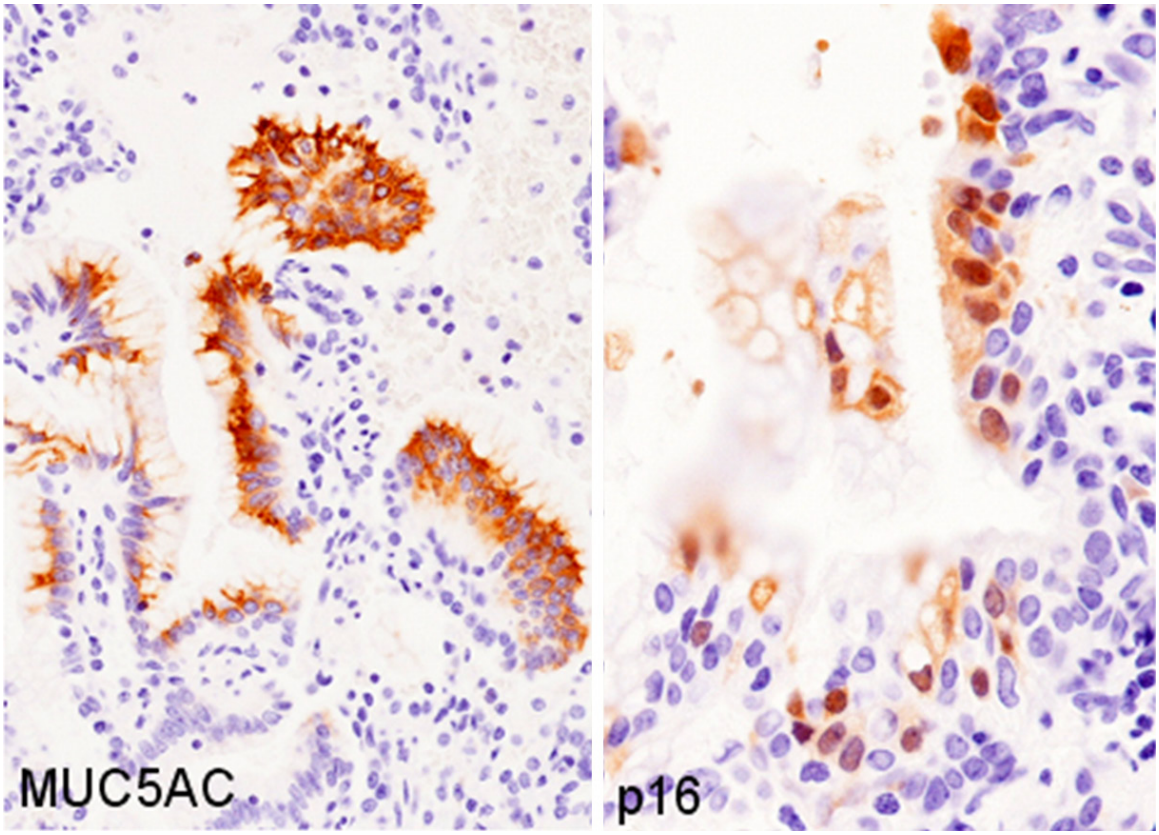

Figure 3. Immunohistochemical features. MUC 5AC and p16 are expressed in the proliferative mucous cells. x 200 (MUC5AC), x 400 (p16).

in type 1 CCAM is a well known phenomenon [4, 8, 9, 24]. Lantuejoul *et al*. analyzed 7 cases of type 1 CCAM [6]. In their series, 3 of these cases had mucinous BAC and 1 case had mixed adenocarcinoma with predominant BAC component [6]. They clearly demonstrated that K-*ras* mutation at codon 12 (GGT-GCT), as seen in the present case, was observed in three cases (2 cases of BAC and 1 case of mixed adenocarcinoma with BAC component), and the same mutation was also observed in the intracystic mucinous cell clusters [6]. Although overexpression of p53 protein was not observed in their BAC and mixed adenocarcinoma cases, $p16^{INK4}$ protein expression was present in 2 cases. Moreover, loss of heterozygosity at $p16^{INK4}$ locus was observed in two of 3 intracystic mucinous cell clusters [6]. According to these results, they concluded that intracystic mucinous cell clusters may be precursors of mucinous BAC [6]. The present case had mucous cell clusters in the cyst wall, which may also have been precursors of mucinous BAC.

Mani *et al*. reported an interesting case of invasive mucinous adenocarcinoma in a 29-year-old female with type 1 CCAM [24]. They documented an entire spectrum from atypical adenomatous hyperplasia to mucinous BAC and invasive adenocarcinoma [24]. Similar cases that showed this spectrum have also been reported [8, 9, 16]. These cases support the concept that malignant transformation progresses from type 1 CCAM to mucous cell/goblet cell hyperplasia to atypical adenomatous hyperplasia to mucinous BAC, resulting in invasive adenocarcinoma.

KRAS is the one of the most commonly mutated genes in adenocarcinoma of the lung [25]. *KRAS* mutation is more commonly observed in mucinous BAC than in non-mucinous BAC, and is increasingly identified in never smokers [26]. *KRAS* mutation occurs most frequently in codon 12 and 13 in exon 1 [25], which were observed in the previously reported BAC cases in type 1 CCAM as well as the present case [6]. Malignant transformation in type 1 CCAM may be strongly associated with this mutation [6].

Mucinous BAC is thought to originate from mucinous bronchiolar cells, whereas non-mucinous BAC represents a heterogeneous group of neoplasms arising from type 2 pneumocytes or Clara cells. Mucinous BAC shows infrequent expression of TTF-1 (Clara cells or type 2 pneumocyte marker) in contrast to other types of adenocarcinoma [27]. Moreover, mucinous BAC typically shows positive immunoreactivity for MUC5AC, which is expressed in the normal goblet cells of the bronchial epithelium, and no expression of MUC2 and cdx-2 [28, 29]. The immunohistochemical characteristics of mucinous BAC of the present case were typical for this type of tumor.

Many clinicians recommend early surgical resection for CCAM to avoid eventual complications, such as pneumonia and rare development of malignancies, even in asymptomatic cases [30, 31]. Moreover, careful histopathological analysis of the resected specimen is also important for the evaluation of malignant lesion, and the presence of mucous cells should be considered as precursors of BAC.

Disclosure of conflict of interest

None.

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