Clinical Case Report

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First case of bronchiolar adenoma lined purely by mucinous luminal cells with molecular analysis

A case report

Shuli Liu, MD[a], Nan Liu, MD[a], Mingming Xiao, MD[b], Liang Wang, MD, PhD[a,*], En-Hua Wang, MD, PhD[a]

Abstract

Rationale: Bronchiolar adenoma (BA) is a newly designated rare entity of the lung, including both the currently designated ciliated muconodular papillary tumor (CMPT) and so-called non-classic CMPT. The most prominent histological feature of BAs is the bilayered cell structures composed of the continuous basal cell layer and the luminal layer which consists of different proportion of mucinous cells, ciliated cells, Clara cells and/or type II pneumocytes. BA purely covered by mucinous cells without other components in the luminal layer has never been reported.

Patient concerns: An 82-year-old female patient was detected a 0.8 cm ground glass nodule in the left lower lobe of the lung.

Diagnoses: The serum levels of tumor markers were normal.

Interventions: The patient underwent a segmentectomy of the left lower lobe.

Outcomes: The postoperative pathological diagnosis was BA. Molecular analysis revealed that the tumor harbored ALK rearrangement and BRAF mutations simultaneously. There was no recurrence in 17 months of follow-up.

Lessons: BA can be lined only by mucinous cells, without any cuboidal and/or ciliated cells in the surface layer. This sets a dangerous pitfall in differentiation diagnosis with invasive mucinous adenocarcinoma especially during intraoperative frozen pathological diagnosis.

Abbreviations: AB-PAS = Alcian blue/periodic acid–Schiff, AIS = adenocarcinoma in situ, BA = bronchiolar adenoma, CMPT = ciliated muconodular papillary tumor, IMA = invasive mucinous adenocarcinoma, SMA = smooth muscle antibody, TTF-1 = thyroid transcription factor-1.

Keywords: ALK, BRAF, bronchiolar adenoma, ciliated muconodular papillary tumor, immunohistochemistry

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The datasets supporting the conclusions of this article are included within the article.

Ethical approval for this study was obtained from the institutional ethic review boards of the First Affiliated Hospital of China Medical University. Writing consent to participate was provided by the patients for the present research.

Informed consents were obtained from the patients for the publication of her case and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

The authors declare that they have no competing interests.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, [b] Department of Pathology, the People's Hospital of Liaoning Province, Shenyang, China.

[*] Correspondence: Liang Wang, Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang 110001, China (e-mail: cmuwangliang@qq.com).

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1. Introduction

Bronchiolar adenoma (BA) is a newly designated entity of benign lung tumor which will be recognized in the upcoming World Health Organization classification in 2020. This entity encompass a spectrum of lesions including both the currently designated ciliated muconodular papillary tumor (CMPT) and so-called non-classic CMPT. The most prominent histological feature of BA is the bilayered cell structures composed of the continuous basal cell layer and the luminal cell layer which consists of different proportion of mucinous cells, ciliated cells, Clara cells and/or type II pneumocytes.[1] Based on the composition of surface cells, BA can be further divided into proximal-type BA and distal-type BAs. The proximal type is lined by ciliated and mucinous cells, in papillary or flat pattern. The distal type is generally flatted, covered by mucinous cells, cuboidal and/or ciliated cells. For this rare entity, the distal-type BA purely covered by mucinous cells has never been reported. This unique and extremely rare case can be easily misdiagnosed as invasive mucinous adenocarcinoma (IMA). Herein, we report this case with a focus of immunohistochemical features and driver gene mutations.

2. Case report

A 81-year-old female patient was initially detected a 0.6 cm ground glass nodule in the left lower lobe of the lung by computed tomography (CT) during healthy examination in June 2017. The nodule grew to 0.8 cm in August 2018, and no enlarged hilar and

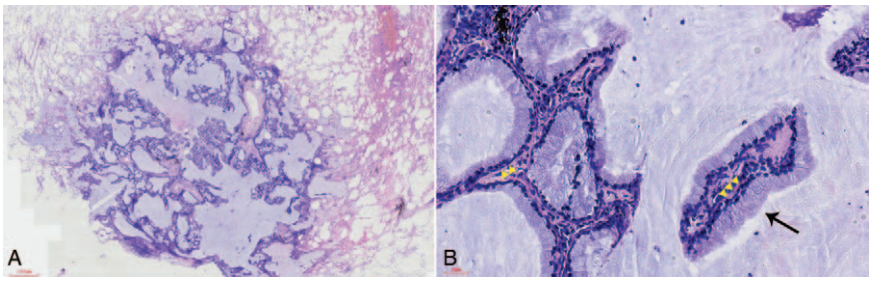

Figure 1. The tumor cells grew along the alveolar walls, with a small number of papillary and adenoid structures, with abundant extracellular mucin (A, 40×). The surface-layered tumor cells were purely tall columnar cells (B, 400×, black arrow) with areas showing bilayered structure (yellow arrowhead) with a continuous basal cell layer.

mediastinal lymph nodes were identified. The serum levels of tumor markers, including carcinoembryonic antigen, neuron-specific enolase, cytokeratin-19 fragment, etc. were normal. The patient underwent a segmentectomy of the left lower lobe, and macroscopical examination revealed a gray-white mucoid mass, measuring 1.0×0.6 cm. An intraoperative frozen pathological diagnosis favored benign mucinous tumor, and deferred to permanent sections to rule out IMA.

Postoperative pathological examination showed the well-circumscribed tumor is located in the lung parenchyma with a maximum diameter of 1.0 cm. The tumor cells grew along the alveolar walls, with a small number of papillary and adenoid structures (Fig. 1A). The luminal tumor cells were purely mild and tall columnar mucinous cells. No ciliated or cuboidal cells could be evident. The nuclei were located in the basal part, which seemed to be arranged in a single layer. However, in certain areas, the tumor was composed of bilayered cellular proliferation with a continuous basal cell layer (Fig. 1B).

Immunohistochemically, the columnar luminal cells were strongly positive for CK7 (Fig. 2A), but negative for thyroid transcription factor-1 (TTF-1). Staining for CK5/6, p40, p63 and TTF-1 revealed an intact and continuous bottom layer of basal cells (Fig. 2B and 2C). The index of Ki-67 was less than 1%. The basal cells were negative for myoepithelial markers, such as S-100, smooth muscle antibody (SMA), and CD117. Alcian blue/periodic acid–Schiff (AB-PAS) staining demonstrated abundant mucin in the cytoplasm of columnar cells and extracellular spaces (Fig. 2D). The final histological diagnosis was rendered as BA. A small panel of driver genes were examined using the ADx-ARMS Kit (Amoy Diagnostics, Xiamen, China). Rearrangement of *ALK* (Fig. 3A) and mutations of *BRAF* (Fig. 3B) were identified. The post-operative course was uneventful, and no recurrence was noted at 17 months' follow-up.

3. Discussion

In 2002, Ishikawa[2] first, described and reported a rare tumor in the peripheral lung and named it as CMPT. CMPT is easily to be misdiagnosed as IMA, therefore it has been widely discussed and concerned in recent years.[3–12] With more and more observation and analysis of CMPT, it is found that the papillary structure, surface ciliated cells and mucinous cells are not absolutely necessary for the diagnosis. Some CMPT-like tumors may present flat growth pattern along the alveolar wall which were covered by Clara and/or alveolar cells on the surface. However, there was always a continuous basal cell layer at the bottom. Therefore,

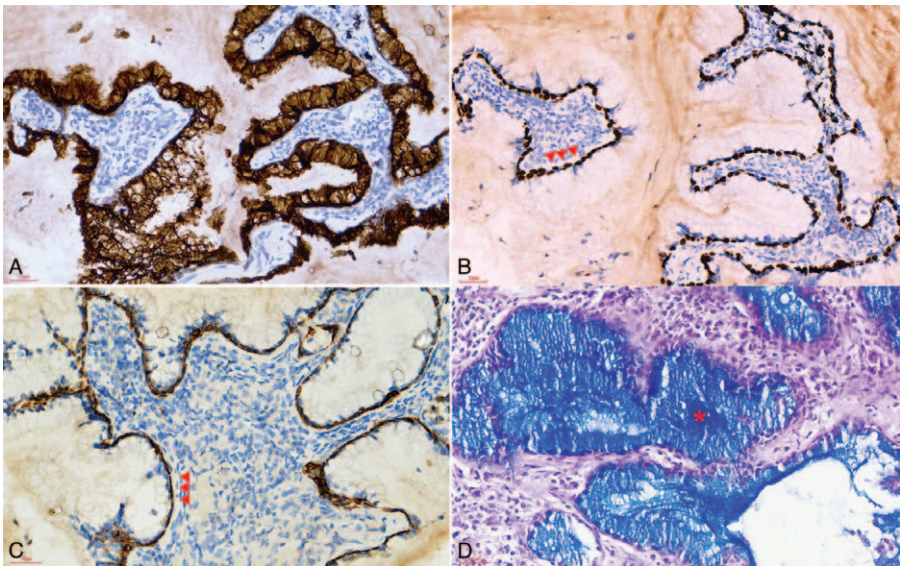

Figure 2. The surface-layered tumor cells were positive for CK7 (A, 400×). The basal-layered tumor cells showed continuous positive staining for p63 (B, 400×, arrowhead) and CK5/6 (C, 400×, arrowhead). AB-PAS demonstrated abundant intracellular and extracellular mucin (D, 400×, asterisk).

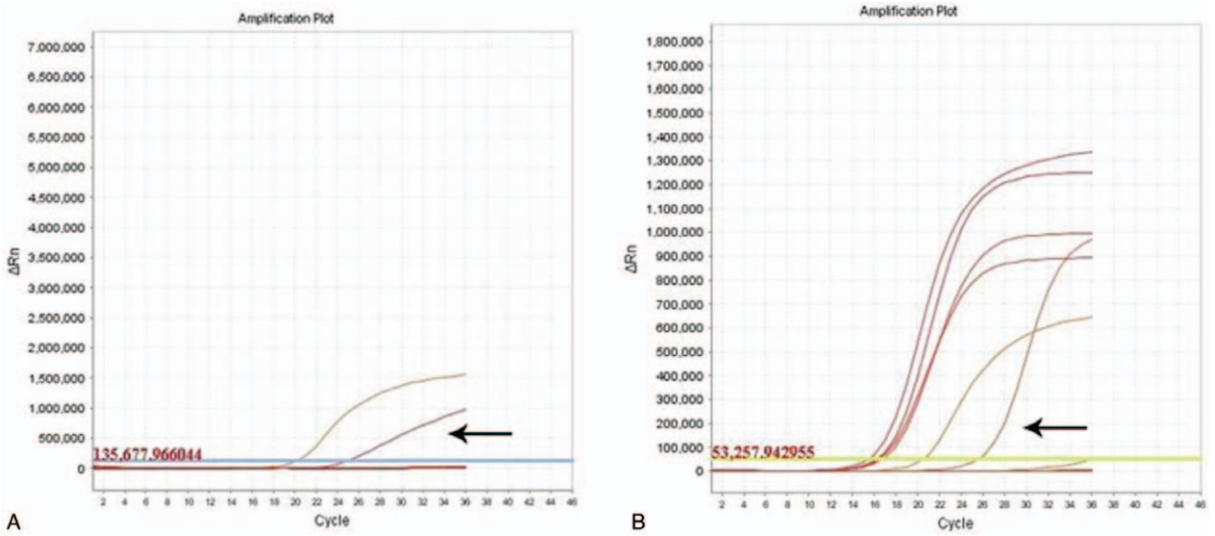

Figure 3. Quantitative reverse-transcript Polymerase chain reaction (qRT-PCR) revealed *ALK* rearrangement (A, arrow) and *BRAF* mutations (B, arrow) in the tumor cells.

cases with papillary structures were named as classic CMPT, while those without papillary structures were proposed as non-classic CMPT.[13] In order to solve this dilemma, Chang, et al carried a well-designed experimental observation, and found that the morphological change and immunophenotype of CMPT, both classic and non-classic types, are essentially consistent with the continuous spectrum of the components of mucous epithelial cells from the proximal to the distal bronchioles. So it is suggested to name these kinds of tumors as the diagnosis name of BA.[1] This convincing work expanded the understanding of CMPT, and BA will be recognized in the upcoming World Health Organization classification in 2020.

Although the recognition of BA has made new progress, there are still some difficulties in its differential diagnosis. For example, the distal BA covered mainly by alveolar cells or Clara cells in the luminal layer needs to be differentiated from adenocarcinoma in situ. Vigorous proliferation of basal cells also needs to be discriminated from sclerosing pneumocytoma. The most challenging situation is the differentiation between BA rich in mucinous cells and IMA, especially in the rapid frozen pathological diagnosis, like the current case. Pathologists need to carefully look for cuboidal and/or ciliated cells to avoid the pitfall. If the luminal layer was purely lined by mucinous cells, pathologist must pay more effort to search areas showing bilayerd composition with the basal layer at the bottom. This is the key lesson we learned from the current case. Another 2 benign tumors, mucinous adenomas and mucinous cystadenomas, also need to be considered in differential diagnosis. These 2 tumors contain only a small number of myoepithelial cells at the bottom layer rather than a continuous basal cell layer, therefore, immunohistochemical staining of myoepithelial markers may contribute to the differential diagnosis.

Driver mutations have been observed in BAs.[1,4,5,7,13,14] In the current study, we demonstrated that this special case harboring 2 different driver mutations simultaneously, which are rarely seen even in adenocarcinoma of the lung. It still needs further study to reveal whether coexistence of multiple driver-gene mutations may lead to worse prognosis.

In conclusion, this case expanded the understanding of BA that the luminal layer can be mucinouse cells alone without any other components, such as cilated cells, cuboid cells clara cells and/or alveolar cells.

Author contributions

SL, EHW and LW analyzed the data and wrote the manuscript. MX performed the immunochemical staining. NL performed genetic analysis. All authors have read and approved the final manuscript.

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