Case Report
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Distal-Type Bronchiolar Adenoma of the Lung. Findings of Intraoperative Cytology and Review of the Literature

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Abstract

Introduction: Bronchiolar adenoma (BA) of the lung is a recently recognized rare benign neoplasm of bronchiolar origin. Because of a lepidic growth pattern in routine histopathologic examination, pathologists often erroneously recognize this lesion as pulmonary adenocarcinoma, atypical adenomatous hyperplasia, peribronchiolar metaplasia, or basal cell hyperplasia in intraoperative frozen section diagnosis. Differential diagnosis from malignancy is especially important.

Case Presentation: We report herein a case of BA which was accurately diagnosed with both intraoperative cytology and frozen histology preparations. A 70-year-old man nonsmoker underwent computed tomography scan, revealing a 7.2 × 6.8 mm-sized solid nodule in the peripheral field of the right lower lobe. Video-assisted thoracoscopic wedge resection of the nodule followed. A localized anterior mediastinal mass was also simultaneously excised, and the diagnosis of B1 thymoma was made. The 7 × 7 × 4 mm-sized, solitary, jelly-like, and well-circumscribed and subpleural located lung mass microscopically revealed a lepidic growing lesion, consisting of non-atypical ciliated cells, mucous cells and basal cells, surrounded by mucin pools. The diagnosis of distal-type BA was made intraoperatively with both cytologic and histologic examinations. Immunohistochemically, the ciliated columnar, mucous, and basal cells were positive for cytokeratin 7 and $p16^{INK4a}$. TTF-1 and napsin A were positive in the ciliated columnar and mucous cells. Mucous cells were focally immunoreactive for MUC5AC. MUC6 was negative. Basal cells were clearly recognized by immunostaining for CK5/6, p40, p63 and podoplanin. Genetic analysis demonstrated mutation of *BRAF*V600E. The postoperative course was uneventful for four months.

Discussion/Conclusion: Previous studies have described difficulty in making a diagnosis of BA, particularly during intraoperative consultations. Appropriate recognition of a two-celled pattern with consistent association of basal cells is critically important for the intraoperative diagnosis of BA. Ultrarapid immunostaining for p40, p63 or CK5/6 using frozen sections may be of diagnostic value.

Keywords: Bronchiolar Adenoma • Distal-type • Cytology • Intraoperative Diagnosis

Abbreviations: BA: Bronchiolar adenoma • TTF-1: Thyroid transcription factor-1 • MUC: Mucin • CK: Cytokeratin • $p16^{INK4a}$: Cyclin-dependent kinase inhibitor p16 • *BRAF*V600E: v-raf murine sarcoma viral oncogene homolog B1 • EGFR: Epidermal growth factor receptor • ALK-1: Anaplastic lymphoma kinase-1

Introduction

Bronchiolar adenoma (BA) is a recently recognized rare benign tumor of bronchiolar origin [1-3], and many pathologists and clinicians are unaware of this lesion. BA is often inappropriately diagnosed because it shows radiographic, gross, and histologic presentations similar to other localized lung disorders, especially to primary pulmonary adenocarcinoma. Improvement of diagnostic accuracy for BA is essentially important both for the surgical treatment and for judging the patient's prognosis. BA reveals an indolent clinical course, as no recurrences or metastases have been reported in patients who underwent surgical resection. Hitherto, a total of 111 cases have been reported across the English, Japanese and Chinese literature, and the number is gradually increasing [1-14]. Recent molecular studies of BA discovered a high frequency of driver gene alterations, including mutations in the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*V600E), epidermal growth factor receptor (*EGFR*), *ROS1* and Kirsten *RAS*(*KRAS*) and Harvey *RAS* genes, as well as anaplastic lymphoma kinase-1 (*ALK*-1) gene rearrangements [1-3,13]. We report herein a rare case of BA of distal type: We made an accurate diagnosis with intraoperative cytology and frozen section histology.

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Case Presentation

Clinical summary

A 70-year-old Japanese male nonsmoker was hospitalized in Shimada General Medical Center, Shimada, Japan, because mediastinal and pulmonary lesions were pointed out during the check-ups for angina pectoris. Chest computed tomography scan revealed a 7.2 × 6.8 mm solid nodule without cavitation or pleural retraction at the peripheral area of the right lower lobe of the lung, as shown in Figure 1. A 12 × 12 mm-sized anterior mediastinal mass was also observed. No radiological and clinical features of interstitial lung disease were recognized. There was neither lymphadenopathy nor intrapulmonary metastasis. Primary lung cancer with thymoma was suspected preoperatively. The intraoperative frozen section diagnosis of the lung nodule was distal-type BA. Video-assisted thoracoscopic wedge resection of the lung tumor with excision of the mediastinal mass was performed **(Figure 1)**. The mediastinal tumor was microscopically typical of thymoma, B1 type. The patient did not receive adjuvant therapy, and is currently doing well, four months after surgery.

Cytologic findings

In intraoperative touch smear cytology preparations of the lung nodule, ciliated columnal cells, mucous columnar cells and basal cells were observed. The

background was mucinous but not necrotic. Neither nuclear pleomorphism nor mitosis was discerned. Immunocytochemistry was performed by applying a cell transfer method. The nuclei of the basal cells were immunoreactive for p40. Representative cytologic appearance including p40 positivity is illustrated in **Figure 2**.

Gross findings

Grossly, the peripheral lung lesion displayed a well-circumscribed, 7 × 7 × 4 mm-sized, grayish tan-colored and gelatinous mass, as displayed in **Figure 3**. No pleural retraction was observed. The resected margins were negative.

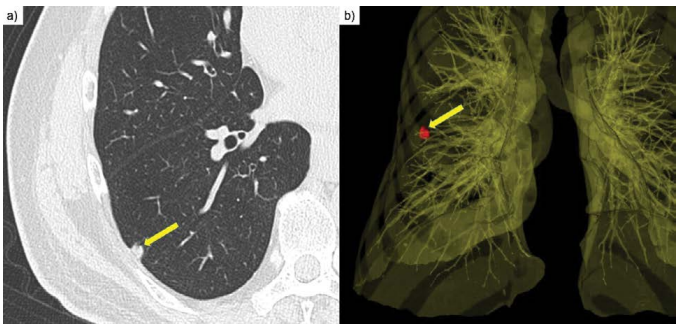

Figure 1. Clinical imaging. **(a)** A chest computed tomography image reveals a 7.2 mm solitary, dense and solid nodule in the subpleural area of the right lower lung lobe (arrow). **(b)** The tumor agitated in red color is penetrated by large bronchiolo-arterial bundles (arrow).

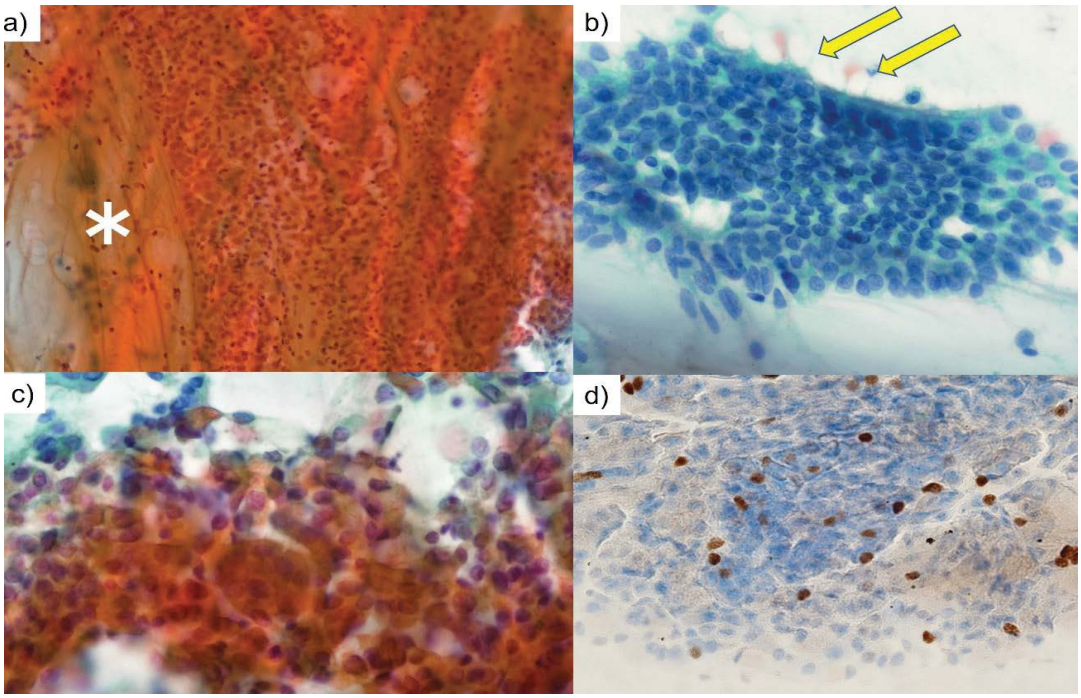

Figure 2. Cytological findings (a-c: Papanicolaou, d: immunocytochemistry for p40). In touch cytology preparations, the background is mucinous (asterisk) and not necrotic **(a)** Numbers of ciliated columnal cells **(b)** and mucous cells can be identified **(c)** Cilia are indicated by arrows. Basal cells immunoreactive for p40 in the nuclei are dispersed **(d)** Nuclear pleomorphism is not discerned, and mitosis is hardly observed.

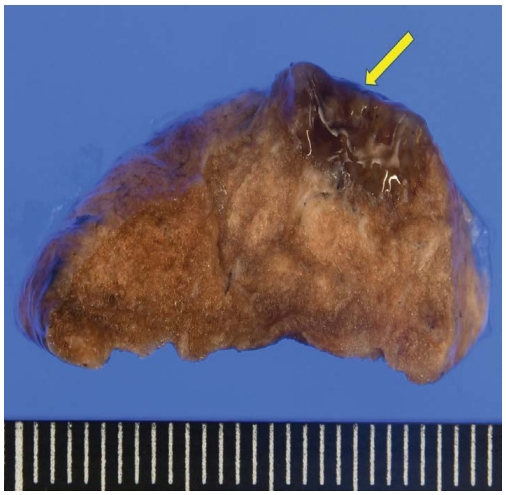

Figure 3. Gross appearance of the wedge-resected lung tumor after formalin fixation. A well-circumscribed, grayish tan-colored, and gelatinous mass measuring 7 × 7 ×4 mm is located just beneath the pleura (arrow). No pleural retraction is seen.

Histological findings

At low-powered magnification, the neoplasm was an unencapsulated, well-demarcated nodule predominantly with glandular architectures, as shown in **Figure 4a**. Mucin was accumulated in both the tumor itself and adjacent alveolar spaces. By imaging analysis, unpaired, medium-sized muscular arteries entering the tumor were observed (**Figure 1b**), indicating peribronchiolar location. Columnar epithelial cells revealed lepidic growth, in association with mild lymphocytic infiltration in the stroma, and they contained cytoplasmic mucin, resembling gastric foveolar or glandular cells, as displayed in **Figure 4b**. The bronchiolar-like epithelial cells displayed a distinct two-layered structure, consisting of both luminal and basal layers. No papillary structures were noted. The tumor cells were devoid of nuclear atypia, mitosis, apoptosis, and necrosis. The luminal layer was composed of ciliated columnar cells and mucous cells, as illustrated in **Figure 4c**: the presence of a continuous layer of basal cells beneath the luminal layer represented the most pathognomonic finding. Immunohistochemically, the ciliated, mucous and basal cells expressed cytokeratin (CK) 7 and cyclin-dependent kinase inhibitor p16 ($p16^{INK4a}$) (clone G175-405). Thyroid transcription factor-1 (TTF-1: clone 8G7G3/1) and napsinA were positive in the luminal-sided ciliated and mucous columnar cells. CK5/6, p40, p63, and podoplanin (clone D2-40) clearly demonstrated the basal cells. Mucin 5AC (MUC5AC) was focally expressed in the apical cytoplasm of the mucous cells. Ki-67 labeling index was 3%. Negative immunohistochemical markers included CK20, carcinoembryonic antigen, HER2/*neu*, MUC2, and MUC6. **Figure 5** illustrates representative immunohistochemical findings.

Molecular analysis

We evaluated gene mutations of *BRAFV*600E, *EGFR*: exons 18, 19, 20 and 21, *ROS1* and *ALK-1* rearrangement. Formalin-fixed, paraffin-embedded samples were submitted for Oncomine Dx Target Test. BRAF V600E mutation was demonstrated.

Discussion

BA was first named by Chang and colleagues in 2018 [1]. According to the intrapulmonary location, BA has been subdivided into proximal and distal types, with most cases being the proximal type. Both types microscopically accompany with a two-layered architecture, composed of luminal cells and continuous basal cells [2,3]. The proximal-type BA is also known as ciliated muconodular papillary tumor that Ishikawa reported the first case in 2002, and the luminal cells are composed of ciliated and mucinous columnar cells [4]. The literature review indicated a total of 111 cases of BA or ciliated muconodular papillary tumor reported to date [1-14]. The tumor size ranged from 2 to 65 mm (mean 9.7 mm and median 8.3 mm). BA was often observed in middle-aged and elderly individuals (mean 65.3 years, median 67 years). The youngest case was a 19-year-old girl [3]. BA has occurred

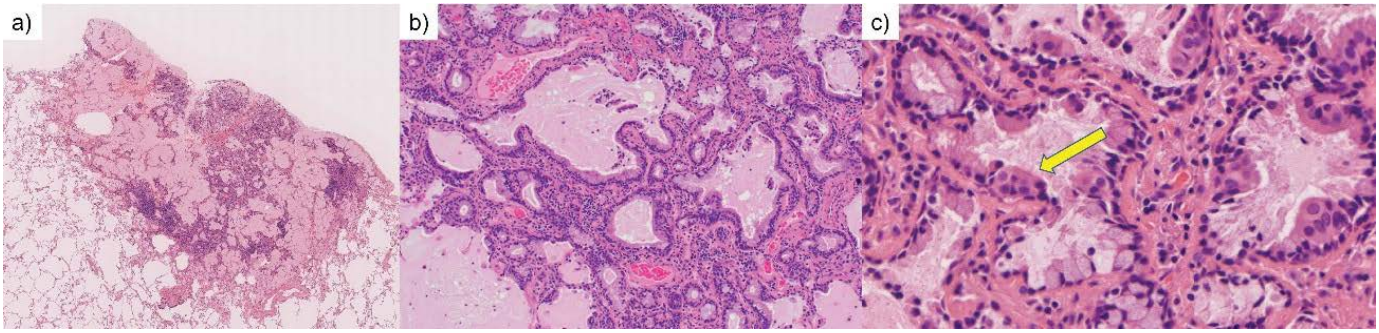

Figure 4. Histological findings (a–c: hematoxylin and eosin staining; a: low-power, b: intermediate-power, c: high-power). (a)The subpleural lung parenchyma is occupied by a defined nodular and mucin-filled lesion. (b) The growing bronchiolar epithelia are associated with mild lymphocytic infiltration in the stroma. Mucin production is observed in the cytoplasm. (c) A high-powered view reveals a two-layered patternof growth: basal cells are consistently distributed beneath the luminal cells. Arrow indicates ciliated cells.

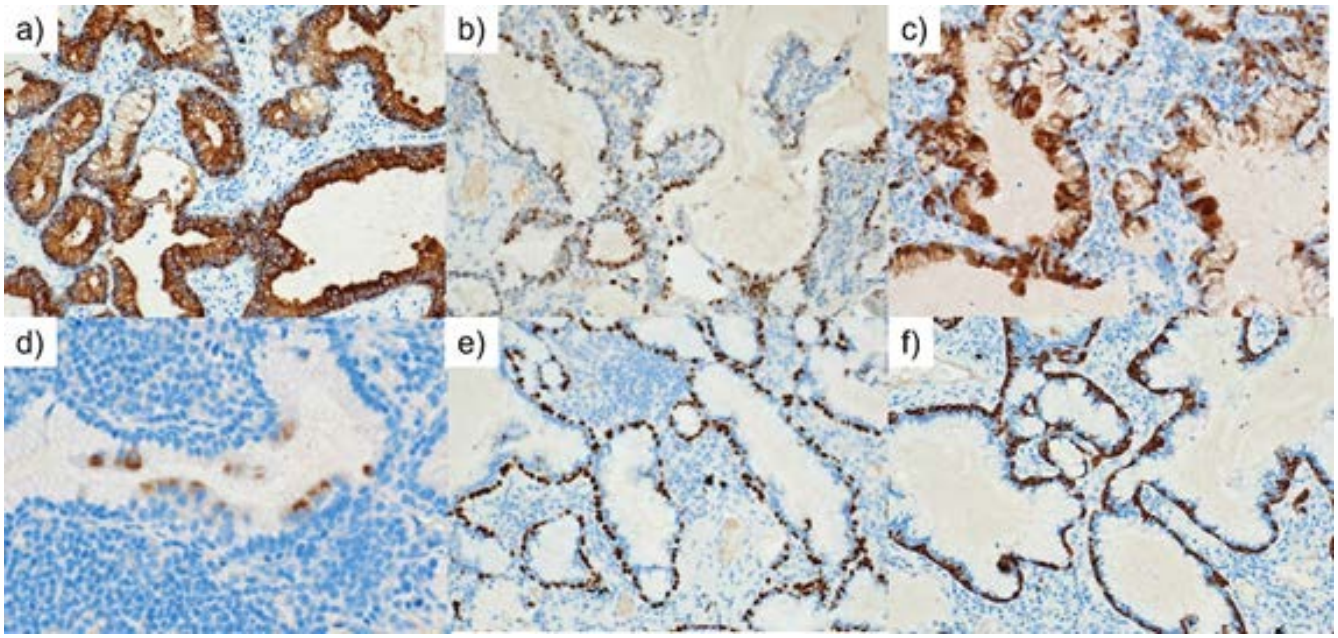

Figure 5. Immunohistochemical findings of the lung tumor. (a) CK7; (b) TTF-1; (c) $p16^{INK4a}$; (d) MUC5AC; (e) p40 and (f) CK5/6. CK7 and $p16^{INK4a}$ are expressed in both the luminal and basal cells. TTF-1 is immunoreactive in the nuclei of luminal-sided cells. Mucous cells are focally and apically immunoreactive for MUC5AC. p40 and CK5/6 clearly decorate the basal cells.

in both men and women, with no preference on the location in the lung. Neither recurrence nor distant metastasis was reported during one-month to 10-years post-operative follow-up periods. BA is an indolent tumor with an exceptionally good prognosis, leading some investigators to have a question whether it is a reactive or hamartomatous lesion. The neoplastic nature of BA has been shown by genetic alterations such as *BRAFV*600E, *EGFR, ALK*-1, *AKT*1 and *KRAS*: in the current case, mutation of *BRAFV*600E was detected. However, these gene alterations are not specific for BA [1-3,13].

To date, BA may be diagnosed inappropriately as adenocarcinoma during intraoperative consultation, leading to lobectomy rather than local wedge resection. Chang, et al [1] described that for nine cases of BA, intraoperative frozen section diagnoses included adenocarcinoma (n=7) and mucous gland adenoma (n=1). One lesion was appropriately diagnosed. According to Shirsat, et al. [10], only 3 (17%) of 18 were correctly diagnosed intraoperatively, all of which were proximal-type BA: The remainders were diagnosed as adenocarcinoma (n=7); invasive mucinous adenocarcinoma (n=1); non-small cell lung carcinoma (n=1); cystic mucinous neoplasm, favor adenocarcinoma (either mucinous or colloid type) (n=1); favor adenocarcinoma, cannot exclude ciliated muconodular papillary tumor (n=1); atypical proliferation (n=2); mucinous epithelial proliferation (n=1); and mucinous gland adenoma (n=1). Guo, et al. [14] reported an accurate diagnosis of BA in frozen sections. In the current case, the frozen sections revealed continuous lepidic growth of columnar cells resembling adenocarcinoma *in situ* or lepidic adenocarcinoma. Noteworthy features included a two-layered structure and very bland nuclei of tumor cells without mitotic activities. Richter, et al. [15] described that ultra-rapid immunostaining for p40, p63 or CK5/6 using frozen sections was extremely helpful for confirming the intraoperative diagnosis of BA.

In the current case, BA of distal type was diagnosed intraoperatively, based upon the same findings as the description by Guo, et al. [14]. We should emphasize that intraoperative cytology was extremely helpful for the accurate diagnosis of BA. In the cytology specimen, ciliated columnal cells, mucous cells, and basal cells without nuclear atypia were identified in the background of mucinous material. Immunocytochemically, p40 was detected in the nuclei of the basal cells.

Conclusion

Despite its rarity, BA should be considered when cytological, histological and immunohistochemical evaluations of a solitary nodule in the peripheral lung reveal non-atypical ciliated, mucous, and basal cells with a mucinous background. To the best of our knowledge, this is the first report that illustrates cytological findings of BA.

Statement of Ethics

All the procedures were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. The patient gave a written informed consent to publication as a case report. The study was approved in October 2021 by the Ethics Committee for Clinical Research of Shimada General Medical Center, Shimada, Shizuoka, Japan (approval number R03-12).

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