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Malignant transformation of pulmonary bronchiolar adenoma into mucinous adenocarcinoma: A case report

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Abstract**BACKGROUND**

Bronchiolar adenoma (BA) and ciliated muconodular papillary tumor (CMPT) are rare tumors that have bilayered cell proliferation and continuous expression of p40 and CK5/6 in the basal cell layer. Diagnosis is difficult because of the limited knowledge of these tumors and their morphological similarities to malignant tumors, including invasive mucinous adenocarcinoma, especially based on the histopathology of intraoperative frozen sections. These tumors are now considered to be benign neoplasms, with malignant transformation reported in only a few cases.

CASE SUMMARY

A 57-year-old woman presented with a 17.0 mm × 7.0 mm nodule in the lower lobe of the left lung. Hematoxylin-eosin staining and immunohistochemistry of a surgical specimen were performed. The tumor consisted of a BA area and a mucinous adenocarcinoma (MA) area. In the BA area, the tumor had a bilayered structure of luminal cells and basal cells. The basal cells were positive for CK5/6 and p40, but the MA area was negative for these biomarkers. The Ki-67 proliferation index was low (1%~2%). The patient was diagnosed with BA accompanied by MA, and had a favorable outcome.

CONCLUSION

The present study indicated that BA may be carcinogenic, and suggests that clinicians should be aware of its potential for malignant transformation.

INTRODUCTION

Chang *et al*^[1] proposed the term bronchiolar adenoma (BA) in 2018 to describe a putatively benign neoplasm that is histologically similar to the bronchial epithelium. These lesions involve the alveolar lung parenchyma instead of the bronchioles. Gross observations indicate they proliferate along the native alveolar wall and have a papillary or flat architecture; microscopic observations indicate they consist of proliferating bilayered cells with luminal cuboidal and goblet cells, and a continual basal cell layer that expresses p40 or CK5/6. Thus, Chang *et al.* considered BA as a broader category that includes ciliated muconodular papillary tumors (CMPTs).

The increasing utilization of high-resolution computed tomography (CT) has led to the detection of a wide array of pulmonary abnormalities, including nodules with a ground-glass appearance or peripheral mucus-secreting characteristics. The limited knowledge of BA/CMPT and its morphologic similarity to malignant tumors, including invasive mucinous adenocarcinoma (IMA), presents a diagnostic challenge, especially in intraoperative frozen sections. We reviewed the available English language literature from 2002 to 2022 and identified only four cases of BA/CMPT with malignant transformation^[2-5]. Thus, much the biological nature and clinical significance of BA/CMPT remain unknown. Herein, we present a patient with mucinous adenocarcinoma (MA) that developed from the malignant transformation of a BA to raise awareness of this disease and improve its diagnosis.

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CASE PRESENTATION

Chief complaints

A 57-year-old female patient presented with a two-year history of a space-occupying pulmonary lesion without any other clinical signs or symptoms.

History of present illness

The patient first received a plain chest CT scan during a physical examination on November 3, 2019. The results indicated a few patches in the lower lobe of the left lung, considered to be an inflammatory disease at that time. A CT reexamination on September 15, 2021 showed that the density of these lesions had increased and the margin was slightly blurred, but it was still considered to be an inflammatory disease. We recommended annual follow-ups at that time. On December 22, 2021, the patient received a high-resolution plain chest CT scan. The results indicated a mixed solid and ground-glass nodule in the posterior basal segment of the lower lobe of the left lung that was approximately 17.0 mm × 7.0 mm, irregular in shape, and close to the pleura. We could not exclude a malignant lesion, and recommended surgery. The patient denied the presence of chest tightness, chest pain, cough, or expectoration, and reported no weight loss.

History of past illness

The patient had no relevant medical history, or habits, such as smoking and drinking.

Personal and family history

The patient denied any relevant family history.

Physical examination

There were no special physical signs.

Laboratory examinations

Routine laboratory blood results were normal.

Imaging examinations

A high-resolution chest CT plain scan showed a 17.0 mm × 7.0 mm nodule in the left lower lobe of the lung (Figure 1).

FINAL DIAGNOSIS

We diagnosed the intraoperative frozen section as a kind of pulmonary epithelial tumor, but it was difficult to differentiate BA from invasive adenocarcinoma, because this requires immunohistochemical examination of paraffin sections. The final diagnosis was mixed BA and MA based on the results of histopathology and immunohistochemistry of the surgical specimen.

TREATMENT

A biopsy with wedge-resection of the lung under video-assisted thoracoscopy was performed. The gross appearance of the resected specimen revealed a 17.0 mm firm, isolated, gray-white nodule of moderate hardness in the lung parenchyma adherent to the pleura.

OUTCOME AND FOLLOW-UP

Hematoxylin-eosin (H&E) staining of the postoperative paraffin section showed the tumor was poorly delineated, closely associated with the bronchioles, and had spread to the adjacent alveolar wall (Figure 2A). In the center of the lesion, the presence of a bilayered structure could be observed—it consisted of tripartite cellular components that were analogous to the bronchiolar-type epithelium, and was comprised mainly of basal cells and luminal epithelial cells (Figure 2A, in yellow dotted lines; Figure 2B-D). The luminal layer was predominantly formed of mucinous, ciliated columnar, and cuboidal or low columnar cells in various numbers and proportions (Figure 2D). These cells were arranged continuously in a flat, papillary, and glandular pattern along the preexisting alveolar wall. Skip lesions of tumor cells along the alveolar wall were observed. The tripartite cellular components were devoid of significant atypia, mitosis,

or necrosis. Most areas in the center of the lesion had a continuous layer of basal cells, but other regions had no evidence of this layer or papillary fronds. However, part of the tumor periphery had some characteristics of an adenocarcinoma (Figures 2A, in black dotted lines), mainly represented by glandular structures lined with tall columnar mucinous cells that proliferated along the alveolar wall, which had mild atypia and low mitotic activity (Figure 3). There were no ciliated cells, but a few basal cells were observed. Skip lesions remained (Figure 3B and 3D), with focal areas of large mucinous cells and abundant mucus secretion.

We used immunohistochemical analysis to detect CK7, TTF-1, napsin A, CK5/6, p40, and Ki-67. The results showed that CK5/6 (Figure 4A) and p40 (Figure 4B) had continuous and consistent expression in basal cells, but discontinuous expression in some cells with a skipping pattern. It was hypothesized that the distal bronchioles could potentially function in gas exchange, and that basal layer cells might be discontinuous as they migrate to the alveolar sacs. The absence of basal cell biomarkers (Figures 5A-D) indicated that basal cells were absent in certain glandular areas. CK7 showed diffuse positivity in basal and luminal cells (Figures 4C and 5E). TTF1 was expressed in basal, ciliated, cubic, and low columnar cells (Figure 4D), but not in mucinous cells (Figures 5F). Expression of napsin A was weak (Figure 4E and 5G), and the Ki-67 proliferation index (1%-2%) was low in cubic and low columnar cells (Figure 4F and 5H).

We finally diagnosed the patient with mixed BA and MA based on pathology, and discharged her 3 days after the operation. She was well and stable, and we considered further work-up unnecessary.

DISCUSSION

The hallmark of BA is a continuous basal cell layer. This feature indicates it is a noncancerous neoplasm^[1] and distinguishes it from lung adenocarcinoma. Under low-power magnification, BA may be misdiagnosed as a preinvasive or invasive carcinoma, especially in frozen sections. However, high-power magnification shows ciliated and basal cells, thus preventing this misdiagnosis^[6]. In the present case, our frozen epithelial

neoplasm sections indicated flat, papillary, and glandular structures, making it difficult to identify it as a benign or malignant lesion.

The diagnosis of BA should be based on morphological and immunohistochemical observations. Chang *et al*^[1] showed that BA has a spectrum of morphologic features that range from the proximal to distal respiratory bronchioles. The proximal type features a bilayered epithelium consisting of continuous basal and luminal epithelial cells (mucinous and ciliated columnar cells); the bilayered bronchiolar proliferation appears as a papillary structure and the luminal cells have no expression or weak expression of TTF-1 and napsin A, and the basal cells have continuous expression of p40 and CK5/6. In contrast, cells in the distal-type BA are not ciliated or mucinous, and a papillary configuration may be absent. Luminal cells express TTF-1 and napsin A, whereas basal cells express p40 and CK5/6 in a skipping pattern.

Our patient's tumor was 17.0 mm in diameter, and had focal areas with a continuous basal cell layer. Significant ciliated differentiation was observed in the luminal cells, accompanied by abundant mucinous cells. However, the basal cell biomarkers had a skipping pattern and lacked a papillary architecture in certain areas. The luminal cells were cuboidal or low columnar cells, and were positive for TTF-1 and napsin A. Thus, the morphological and immunohistochemical features of the lesion were consistent with proximal to distal bronchiolar changes in the mucosal epithelial cells.

Although the 2021 WHO classification considers BA as a benign tumor, other evidence suggests that BA has malignant potential^[1,7-13]. The high prevalence of mutations in certain driver genes (*EGFR*, *BRAF*, *ALK*, and *KRAS*)^[1,8,12,14,15] suggests these lesions are neoplastic rather than reactive or metaplastic. However, the association of these mutated genes with BA pathogenesis and prognosis remains uncertain and requires further investigation.

Four previous publications reported patients who had BA/CMPT with malignant transformation (Table 1)^[2-5]. Miyai and collaborators^[2] presented a case of CMPT with malignant transformation of basal cells. Chen and colleagues^[3] reported a case of MA

resulting from CMPT, and speculated that CMPT was a precursor of MA. Han and co-workers^[4] presented a unique case with loss of the continuous basal cell layer at the junction between BA and IMA, although the BA and IMA had the same *KRAS* mutations. Wang *et al*^[5] also described a patient with malignant CMPT. We used H&E staining and immunohistochemistry to diagnose our patient as having MA caused by the malignant transformation of BA, thus providing histological evidence of the malignant potential of BA. Ultimately, a common feature of all these cases is the absence of the basal cell layer.

Several gene mutations that drive lung adenocarcinoma also occur in BA. The high incidence of *BRAF* mutations in CMPT (50%)^[14] contrasts with *EGFR* mutations in lung adenocarcinoma. Mutations of *EGFR*, *AKT1*, *KRAS*, and gene rearrangement of *ALK* can also occur in BA^[12,14,15]. Zheng *et al*^[16] used the term “classic CMPT” to refer to a lesion with tripartite cellular constituents, including ciliated columnar cells, mucinous cells, and basal cells with predominantly papillary architecture. Compared with the non-classic CMPT, the frequency of *BRAF* mutations is higher in classic CMPT. However, Chang and collaborators^[13] reported that *BRAF* mutations were more frequent and common in distal-type BA.

CONCLUSION

Postoperative pathological findings in our patient confirmed the presence of mixed BA and MA, with the latter's underlying etiology suspected to be from the malignant potential of BA. Examination of the pathological morphological characteristics of frozen sections makes it difficult to differentiate BA from adenocarcinoma, because it is difficult to observe basal cells in these sections. Therefore, we suggest that pathologists should increase their knowledge of BA to reduce the probability of misdiagnosis and missed diagnosis.

ACKNOWLEDGEMENTS

The authors thank the patient for allowing her case to be presented.

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