

Case Report

Adenoid cystic carcinoma of the right main bronchus showing squamous differentiation and mimicking mucoepidermoid carcinoma: a case report

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Received February 7, 2015; Accepted April 10, 2015; Epub May 1, 2015; Published May 15, 2015

Abstract: Complete dissection of tracheobronchial adenoid cystic carcinoma (TACC) by surgery alone is sometimes difficult and has a greater propensity than tracheobronchial mucoepidermoid carcinoma (TMEC) for its surgical margin to become positive. In addition, TACC is more likely to present distant metastases than TMEC. Considering these facts, TACC and TMEC should be differentiated based on histopathological examination of biopsy specimens. Herein, we present a case of 54-year-old woman with a tumor in the right main bronchus, whose biopsy specimen was difficult to diagnose as TACC or TMEC. The specimen from the rounded protrusion of the tumor showed squamous differentiation, along with the presence of glandular and basaloid cells, making morphological examination alone ineffective in rendering a definite diagnosis. Thus, the addition of immunohistochemical analysis, α SMA and CD43 expression in basaloid cells and c-kit expression in glandular cells, was useful for accurately diagnosing TACC in this case. The squamous component was considered to be neoplastic because of its increased expression of cyclin D1 and overexpression of p16. The surgically resected specimen contained typical morphology of ACC, and the diagnosis of TACC was definitely confirmed.

Keywords: Bronchus, adenoid cystic carcinoma, mucoepidermoid carcinoma, squamous differentiation, immunohistochemistry

Introduction

Tracheobronchial adenoid cystic carcinoma (TACC), which originates from the mixed seromucinous glands in the tracheobronchial submucosa, is unlikely to be identified at an early stage [1]. Complete dissection of TACCs by surgery alone are sometimes difficult due to their submucosal spread and perineural invasion; longitudinal extension along the tracheobronchial tree that is greater than axial extension [1-3], and the risk that the surgical margin becomes positive [1].

In regard to the frequency of tracheobronchial salivary gland-type carcinoma, tracheobronchial mucoepidermoid carcinoma (TMEC) is most often encountered followed by TACC [4]. TMEC usually presents with a well-circumscribed lesion with an intraluminal rounded protrusion without diffuse bronchial wall spread [5]. TACC only occasionally exhibits an intraluminal rounded protrusion [3]. Since the prognosis of TACC is poorer than that of TMEC, with TACC having a

greater propensity to present distant metastases [6] and a positive status of surgical margins due to bronchial wall spread [1], it is critical that these two carcinomas are differentiated based on histopathological examination of biopsy specimens.

Herein, we present a case of TACC with an intraluminal rounded protrusion arising in the right main bronchus. In a biopsy specimen, the surface of the protrusion was found to be covered by neoplastic epithelium with squamous differentiation. However, it was difficult to definitely diagnose this as adenoid cystic carcinoma (ACC) owing to macroscopic and microscopic similarities to mucoepidermoid carcinoma (MEC). To the best of our knowledge, this is the first reported case of ACC, at least TACC, with squamous differentiation.

Clinical summary

A 54-year-old woman presented with complaints of severe cough and wheezing. The

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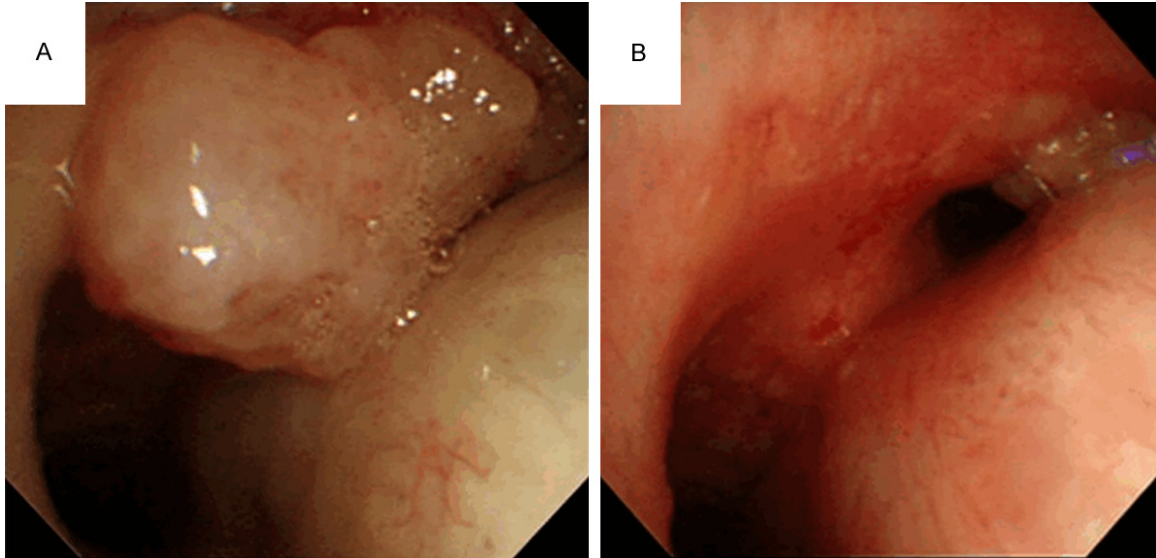


Figure 1. Bronchoscopy. A. A rounded protrusion almost occluded the right main bronchus. B. Following radiation therapy, the opening of the right main bronchus was observed.

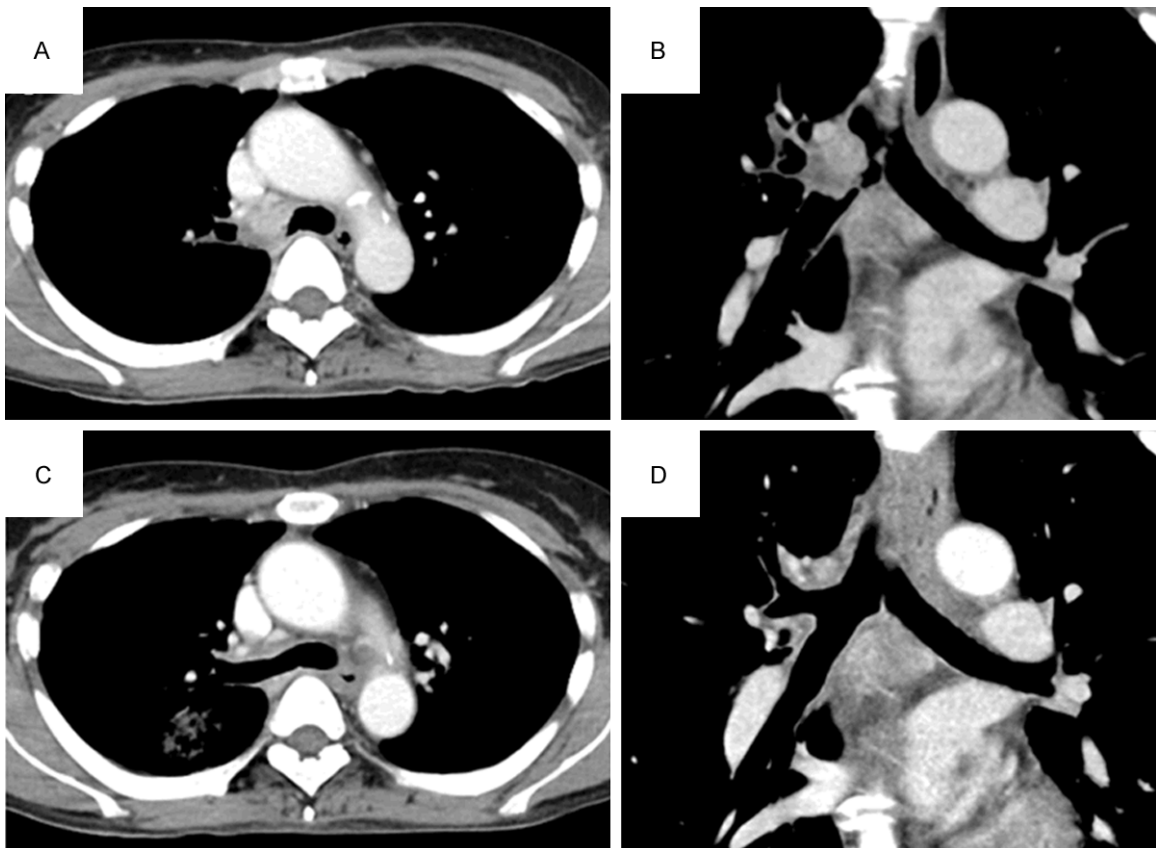
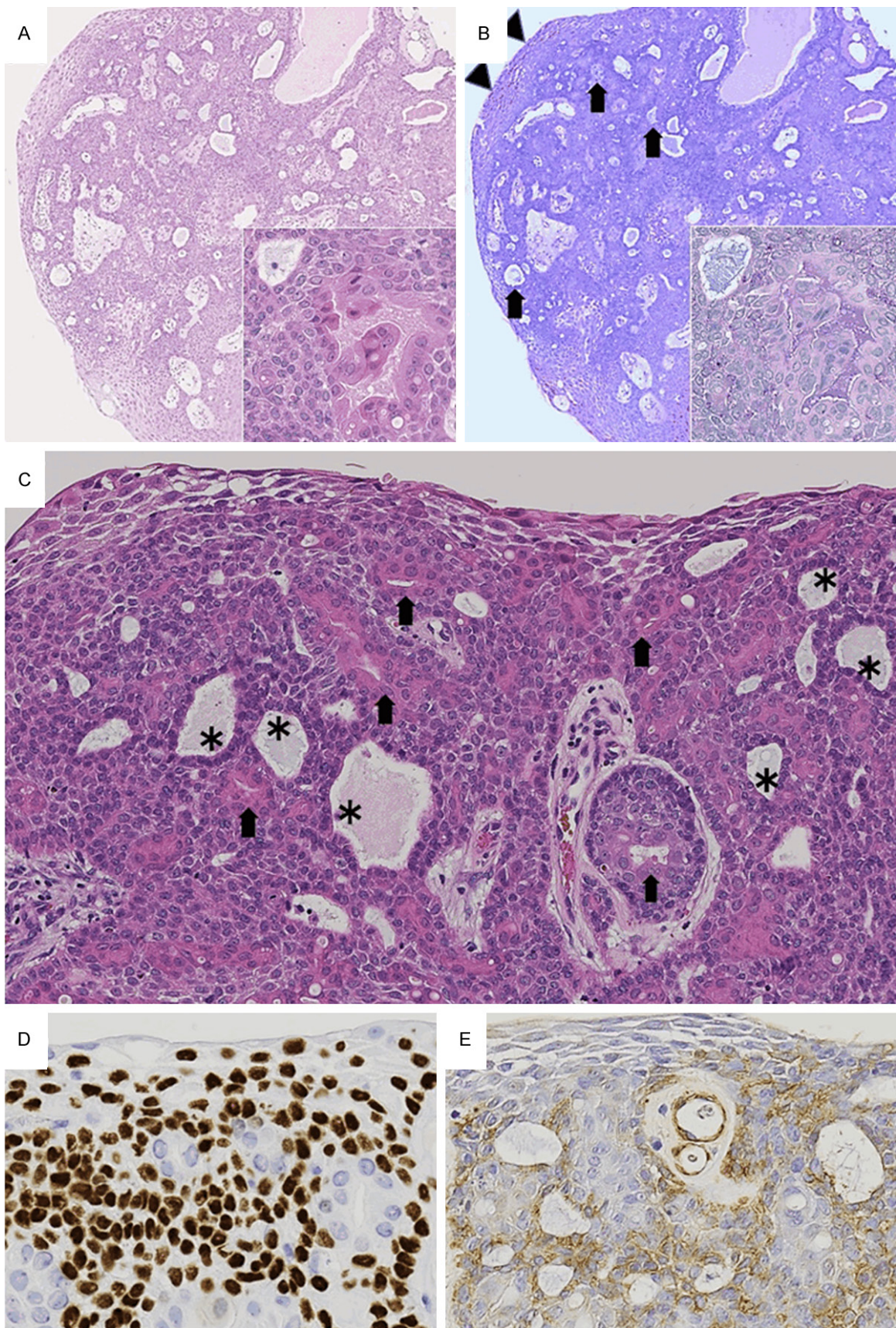


Figure 2. Contrast-enhanced computed tomography. A, C. Axial; B, D. Coronal. A, B. Moderately enhanced tumor was located in the right main bronchus. C, D. Following radiation therapy, a significant reduction of tumor size was observed.

chest radiograph was unremarkable. Although inhaled corticosteroids and bronchodilators

had been administered for 1 year to treat suspected asthma, they were ineffective. Com-

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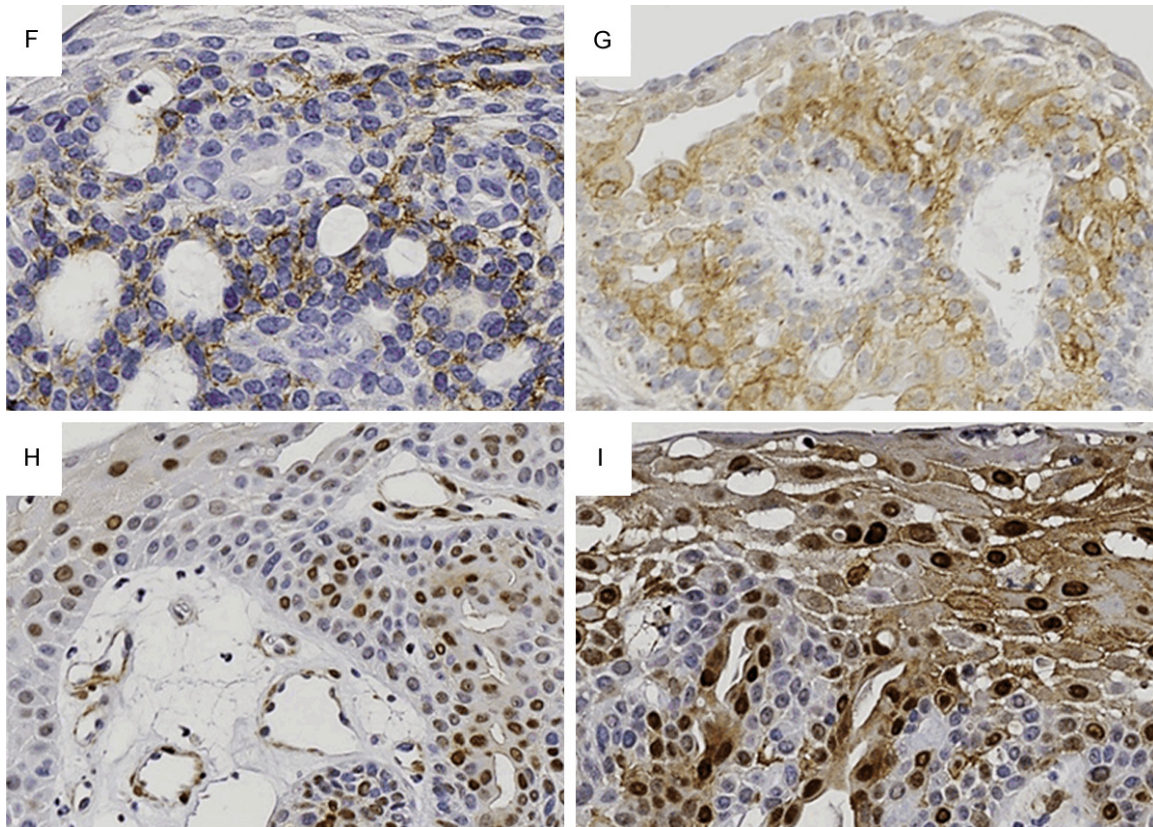


Figure 3. Microscopic and immunohistochemical findings of a biopsy specimen. A. A mixed squamous and glandular lesion is observed ($\times 20$). Inset: true gland lined by glandular cells and pseudogland lined by basaloid cells ($\times 400$). B. Periodic acid-Schiff-alcian blue (PAS-AB) staining shows PAS-positive glycogen in the region with squamous cells (arrow heads) and an AB-positive pseudoglandular structures (arrows) ($\times 20$). Inset: some true glands are PAS-positive in contrast to the AB-positive pseudoglandular structures ($\times 400$). C. True glands (arrows) are surrounded by monolayer to multilayer basaloid cells. These complexes are continuous each other and gradually transit to the surface squamous cells ($\times 400$). Asterisks indicate pseudoglands. D. Positivity of basaloid cells and squamous cells for p63 ($\times 400$). E. Positivity of basaloid cells for α SMA ($\times 400$). F. Positivity of basaloid cells for CD43 ($\times 400$). G. Positivity of c-kit for the majority of the glandular cells, and focally for basaloid cells ($\times 400$). H. Increased immunoreactivity of cyclin D1 in glandular and squamous cells, with lesser reactivity to basaloid cells ($\times 400$). I. Overexpression of p16 in glandular and squamous cells with lesser reactivity to basaloid cells ($\times 400$).

puted tomography (CT) was then conducted, revealing a mass in the right main bronchus (RMB). Bronchoscopy revealed a rounded protrusion, almost occluding the RMB (**Figure 1A**). A biopsy was performed, and the most likely histopathological diagnosis was ACC. Lymph node metastasis and distant metastasis were not identified on contrast-enhanced CT, and there was no evidence of a salivary gland tumor; the tumor itself displayed moderate enhancement (**Figure 2A, 2B**). Bronchoscopic argon plasma coagulation (APC) was performed to prevent the obstruction of the RMB, but the tumor was too large to be reduced by APC alone. Radiation therapy was then considered in order to reduce the tumor volume and to increase the safe surgical margin. It included

administration of 40 Gy of radiation in 20 fractions to the local site. The symptoms improved remarkably. Contrast-enhanced CT showed significant tumor size reduction (**Figure 2C, 2D**); bronchoscopy revealed opening of the RMB (**Figure 1B**). Subsequently, sleeve resection of the right upper lobe was performed. Histopathological examination revealed ACC; the surgical margins were free of ACC. The post-operative course was uneventful, and the patient has been recurrence-free for 1 year.

Pathological findings

Initial microscopic examination of the biopsy specimen from the intraluminal rounded protrusion revealed a mixed squamous and glandular

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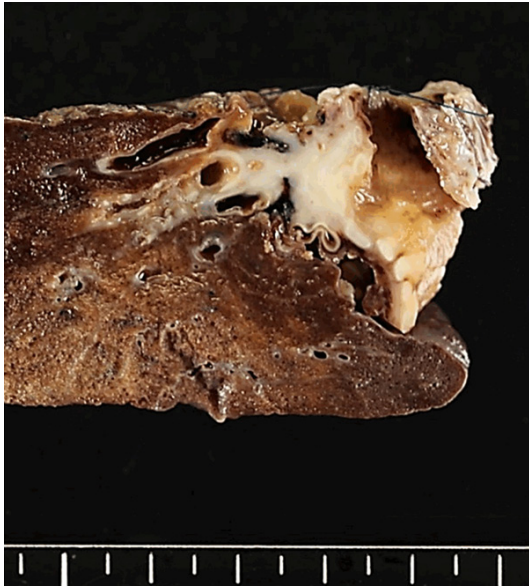


Figure 4. Gross findings of a surgically resected specimen. The surgically resected specimen reveals a whitish lesion centered in the right main bronchus, with spreading along the bronchial tree.

lesion (**Figure 3A**). There were two types of glands: true glands lined by glandular cells and pseudoglands lined by basaloid cells (**Figure 3A**, inset). Periodic acid-Schiff-alcian blue (PAS-AB) staining demonstrated PAS-positive glycogen in the region of the lesion with squamous cells, and AB-positive pseudoglands (**Figure 3B**). Some true glands were PAS-positive in contrast to AB-positive pseudoglands (**Figure 3B**, inset). The true glands were surrounded by monolayer to multilayer basaloid cells; these complexes were continuous with each other and gradually transitioned to the surface squamous cells (**Figure 3C**). Nuclear atypia in glandular, basaloid, and squamous cells was mild, and mitotic figures were not apparent. The presence of pseudoglands accompanied by the lack of cytoplasmic mucin-containing cells typically observed in MEC suggested that this lesion was an unusual form of ACC showing squamous differentiation. To confirm this diagnosis, immunohistochemistry (IHC) was performed.

Upon IHC, basaloid and squamous cells were positive for p63 (4A4, 1:100; Dako, Glostrup, Denmark) (**Figure 3D**). Basaloid cells were also positive for α SMA (1A4, 1:100; Dako) (**Figure 3E**) and CD43 (NCL-MT1, 1:50; Novocastra, Newcastle, UK) (**Figure 3F**). C-kit (polyclonal,

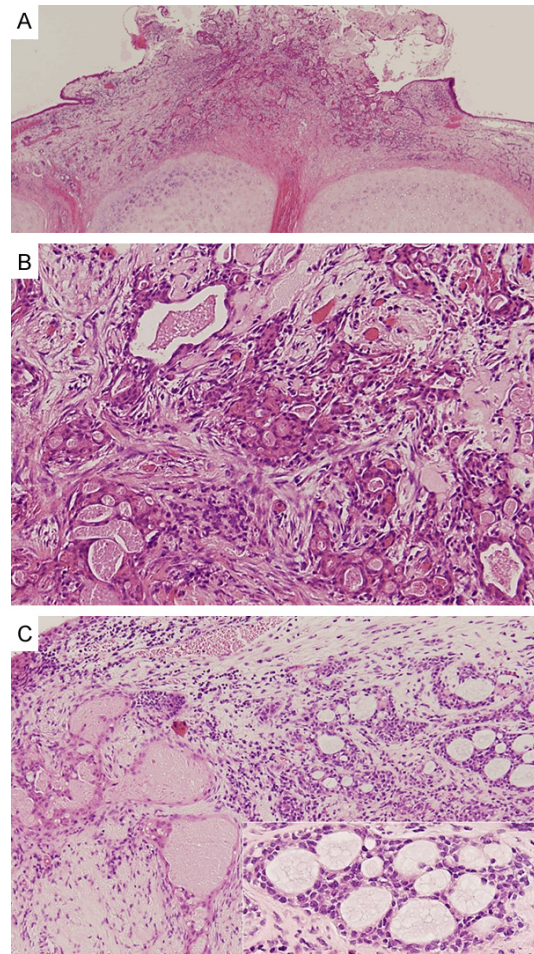


Figure 5. Microscopic findings of a surgically resected specimen. A. Remnant of the rounded protrusion is observed ($\times 12.5$). B. Most of the tumor cells inside the protrusion are non-viable, with increased cytoplasmic eosinophilia and nuclear pyknosis; tubular or cribriform pattern of growth is speculated ($\times 200$). C. Viable tumor cells are observed, with tubular or cribriform growth pattern (right side of the micrograph); non-viable tumor nests are present (left side of the micrograph) ($\times 100$). Inset: typical cribriform growth pattern observed in the viable tumor component ($\times 400$).

1:400; Dako) was positive for the majority of the glandular cells, and was focally positive for basaloid cells (**Figure 3G**). Cyclin D1 (EP12, 1:100; Dako) showed increased staining in glandular and squamous cells, and, to a lesser extent, in basaloid cells (**Figure 3H**); p16 (6H12, 1:100; Novocastra) was considered to be over-expressed in the former two types of cells with lesser reactivity to basaloid cells (**Figure 3I**). Ki-67 (MIB-1, 1:100; Dako) labeling index was less than 5% (not shown). Basaloid cells were interpreted as having myoepithelial features

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because of their expression of α SMA. This finding, along with CD43 expression in basaloid cells and diffuse c-kit expression of glandular cells, rendered the most probable diagnosis as ACC. Increased expression of cyclin D1 and overexpression of p16 in squamous cells are not physiological phenomena. Therefore, the squamous cells were considered to be derived from ACC. Hence, the diagnosis of ACC with squamous differentiation was most valid.

The surgically resected specimen revealed a whitish lesion centered in the right main bronchus, with spread along the bronchial tree (**Figure 4**). The intraluminal rounded protrusion was not detectable due to the effect of radiation therapy.

Microscopically, a remnant of the rounded protrusion was observed (**Figure 5A**). While most of the tumor cells inside the protrusion were non-viable, with increased cytoplasmic eosinophilia and nuclear pyknosis, tubular or cribriform pattern of growth was speculated (**Figure 5B**). Viable tumor cells were observed in patchy distribution with tubular or cribriform growth pattern (**Figure 5C**). Squamous metaplasia of the bronchial surface epithelium was not observed. The surgical margin was free of ACC.

Discussion

ACC usually comprises myoepithelial cells with various degrees of glandular cells, and is identified based on its characteristic architectures: tubular, cribriform, or solid [7]. In this case, the biopsy specimen did not exhibit these characteristic architectures. Although the specimen resembled tubular or cribriform architecture, it would be more appropriate to describe the pattern as anastomosing or fused tubular since each tubule was composed of a central glandular epithelium and an outer monolayer to multilayer of basaloid cells, which were not discrete, but continuous. On the other hand, MEC is defined as the presence of mucin-containing cells intermingled with epidermoid and intermediate cells in variable proportions. According to the Brandwein grading system, MEC is graded from low to high, with intermediate grade the most predominant [6, 8]. Although TMEC usually shows squamous differentiation irrespective of its grade, TACC is not likely to show squamous differentiation. Thus, the findings in

the biopsy specimen of our case are highly unusual.

IHC strongly supported the diagnosis of ACC in the biopsy specimen. CD43, a sialoglycoprotein whose expression is typically seen in T cells and histiocytes, has been reported to be expressed among salivary gland-type tumors, particularly in ACC [9]. Its expression is typically seen in the basaloid cells of tubular or cribriform architectures of ACC [9]. CD43 expression was observed in the basaloid cells comprising the outer layer of the tubule in our case and contributed to the diagnosis. The expression pattern of c-kit is different among tubular, cribriform, and solid ACC, with tubular and cribriform ACC showing c-kit expression - particularly in the glandular cells [10]. Although this was also observed in our case, and was useful to verify the diagnosis of ACC, it could not be used as a single marker of confirmation. This is because not only ACC, but also MEC, express c-kit, as is true in some other salivary-type tumors [11].

Squamous differentiation, which is not usually expected in ACC, made the diagnosis of ACC somewhat challenging. The increased expression of cyclin D1 and overexpression of p16 are found in many cases of ACC [12]. These findings were also observed in the squamous cells of our case, indicating that they shared immunohistochemical characteristics with ACC. Hence, the neoplastic nature of the squamous cells was supported in this case, consistent with squamous differentiation of ACC.

In conclusion, we reported an unusual case of TACC showing squamous differentiation. Because TACC in our case morphologically mimicked TMEC in biopsy specimens, the accurate distinction between TACC and TMEC included immunohistochemical analysis, especially the evaluation of α SMA, CD43, and c-kit. For confirming the neoplastic nature of squamous cells, immunohistochemical analyses of cyclin D1 and p16 were helpful.

Disclosure of conflict of interest

None.

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References

- [1] Huo Z, Meng Y, Wu H, Shen J, Bi Y, Luo Y, Cao J and Liang Z. Adenoid cystic carcinoma of the tracheobronchial tree: clinicopathologic and immunohistochemical studies of 21 cases. *Int J Clin Exp Pathol* 2014; 7: 7527-7535.
- [2] Xu LT, Sun ZF, Li ZJ, Wu LH, Zhang ZY and Yu XQ. Clinical and pathologic characteristics in patients with tracheobronchial tumor: report of 50 patients. *Ann Thorac Surg* 1987; 43: 276-278.
- [3] Kwak SH, Lee KS, Chung MJ, Jeong YJ, Kim GY and Kwon OJ. Adenoid cystic carcinoma of the airways: helical CT and histopathologic correlation. *AJR Am J Roentgenol* 2004; 183: 277-281.
- [4] Zhu F, Liu Z, Hou Y, He D, Ge X, Bai C, Jiang L and Li S. Primary salivary gland-type lung cancer: clinicopathological analysis of 88 cases from China. *J Thorac Oncol* 2013; 8: 1578-1584.
- [5] Li X, Zhang W, Wu X, Sun C, Chen M and Zeng Q. Mucoepidermoid carcinoma of the lung: common findings and unusual appearances on CT. *Clin Imaging* 2012; 36: 8-13.
- [6] Molina JR, Aubry MC, Lewis JE, Wampfler JA, Williams BA, Midthun DE, Yang P and Cassivi SD. Primary salivary gland-type lung cancer: spectrum of clinical presentation, histopathologic and prognostic factors. *Cancer* 2007; 110: 2253-2259.
- [7] Moran CA, Suster S and Koss MN. Primary adenoid cystic carcinoma of the lung. A clinicopathologic and immunohistochemical study of 16 cases. *Cancer* 1994; 73: 1390-1397.
- [8] Roden AC, Garcia JJ, Wehrs RN, Colby TV, Khor A, Leslie KO and Chen L. Histopathologic, immunophenotypic and cytogenetic features of pulmonary mucoepidermoid carcinoma. *Mod Pathol* 2014; 27: 1479-1488.
- [9] Cheuk W and Chan JK. Advances in salivary gland pathology. *Histopathology* 2007; 51: 1-20.
- [10] Ahmed MM and Abo-Hager EA. Differential expression of c-kit and CD43 in histological subtypes of adenoid cystic carcinoma of salivary gland. *Saudi Dent J* 2010; 22: 27-34.
- [11] Salehinejad J, Mohtasham N, Bagherpour A, Abbaszadeh-Bidokhty H and Ghazi A. Evaluation of c-kit protein (CD117) expression in common salivary gland neoplasms. *J Oral Maxillofac Pathol* 2014; 18: 177-182.
- [12] Jour G, West K, Ghali V, Shank D, Ephrem G and Wenig BM. Differential expression of p16(INK4A) and cyclin D1 in benign and malignant salivary gland tumors: a study of 44 Cases. *Head Neck Pathol* 2013; 7: 224-231.