Human Pathology (2013) **44**, 1700–1703

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Case study

# Dedifferentiated adenoid cystic carcinoma of the trachea: a case report with respect to the immunohistochemical analyses of mammalian target of rapamycin pathway proteins

**Mitsuaki Ishida MD, PhD*, Hidetoshi Okabe MD, PhD**

*Department of Clinical Laboratory Medicine and Division of Diagnostic Pathology, Shiga University of Medical Science, Shiga, Japan*

Received 5 September 2012; revised 16 December 2012; accepted 19 December 2012

**Keywords:**
Adenoid cystic carcinoma;
Dedifferentiated carcinoma;
Trachea;
mTOR pathway

**Summary** Dedifferentiated adenoid cystic carcinoma is an extremely rare and highly aggressive tumor. We describe the first reported case of dedifferentiated adenoid cystic carcinoma of the trachea and analyze the expression profiles of mammalian target of rapamycin pathway proteins. A 66-year-old Japanese man was incidentally found to have stenosis of the trachea, and a bronchial biopsy revealed low-grade adenoid cystic carcinoma. The resected specimen revealed dedifferentiated adenoid cystic carcinoma, which was composed of conventional low-grade adenoid cystic carcinoma with tubular and cribriform patterns, and a dedifferentiated carcinoma component (poorly differentiated adenocarcinoma). Immunohistochemical study showed that mammalian target of rapamycin and 4E-BP1 were expressed in both components; however, phosphorylated 4E-BP1 was expressed only in the dedifferentiated carcinoma component. This report clearly demonstrates that mammalian target of rapamycin pathway proteins were activated in dedifferentiated carcinoma. Mammalian target of rapamycin is a central protein involved in carcinogenesis, and administration of its inhibitors prolonged survival in some types of carcinoma. Therefore, mammalian target of rapamycin inhibitors may be a potential candidate for treatment of this highly aggressive carcinoma.


## 1. Introduction

Adenoid cystic carcinoma (ACC) is a distinct type of carcinoma arising in the major and minor salivary glands as well as less commonly in the seromucinous glands of the upper respiratory tract. *Dedifferentiation* is defined as the abrupt transformation of a low-grade or well-differentiated tumor into a tumor of high-grade component without spectrum from original tumor. Albeit extremely rare, dedifferentiation in low-grade ACC has been reported. It occurs preferentially in the seromucinous glands of the upper respiratory tract as well as the salivary gland, but it has also been reported to occur in the lacrimal gland and breast [1-9]. Herein, we describe the first reported case of dedifferentiated ACC of the trachea and analyze the expression profiles of mammalian target of rapamycin (mTOR) pathway proteins in relation to this disease.

* Corresponding author. Department of Clinical Laboratory Medicine and Division of Diagnostic Pathology, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, 520-2192, Shiga, Japan.
*E-mail address:* mitsuaki@belle.shiga-med.ac.jp (M. Ishida).

0046-8177/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.humpath.2012.12.015

## 2. Materials and methods

The formalin-fixed, paraffin-embedded tissue blocks of the resected tracheal tumor specimens were cut into 3-$\mu$m-thick sections, deparaffinized, and rehydrated. Each section was stained with hematoxylin and eosin and then used for immunostaining. Immunohistochemical analyses were performed using an autostainer (Benchmark XT system; Ventana Medical System, Tucson, AZ) according to the manufacturer's instructions. The primary antibodies used in this study are shown in the Table.

## 3. Case report

### 3.1. Clinical findings

A 66-year-old Japanese man with a history of paroxysmal supraventricular tachycardia was incidentally found to have stenosis of the trachea by chest x-ray. Computed tomography demonstrated a stenosis and thickness of the lower tracheal wall involving the bilateral bronchus (Fig. 1). Bronchial biopsy revealed low-grade ACC without any high-grade carcinoma component. Thus, resection of the tracheal tumor and tracheoplasty were performed. No distant metastatic lesions were detected by systemic computed tomography and magnetic resonance imaging analyses.

The postoperative course was uneventful, and no recurrence has been observed during 3 months of medical follow-up.

**Table** Antibodies and summary of immunohistochemical results

| Antibody | Source | ACC | DC |
|---|---|---|---|
| Cytokeratin (AE1/AE3) | DAKO | + | + |
| α-Smooth muscle actin | Novocastra | + | − |
| S-100 protein | Nichirei | + | Focally + |
| Carcinoembryonic antigen | DAKO | Focally + | Focally + |
| Glial fibrillary acidic protein | DAKO | − | − |
| Gross cystic disease fluid protein-15 | Novocastra | − | − |
| Androgen receptor | Novocastra | − | − |
| HER2/*neu* | DAKO | − | + |
| p53 protein | Novocastra | − | + |
| Cyclin D1 | Nichirei | Focally + | + |
| mTOR | Cell Signaling | + | + |
| 4E-BP1 | Cell Signaling | + | + |
| p4E-BP1 | Cell Signaling | − | + |
| Ki-67 labeling index (%) | DAKO | 8.7 | 34.6 |

Abbreviations: ACC, low-grade adenoid cystic carcinoma component; DC, dedifferentiated carcinoma component.

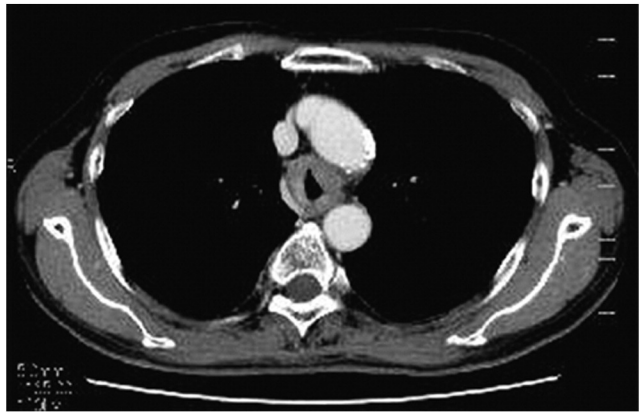

**Fig. 1** Contrast-enhanced computed tomography showing a stenosis and thickness of the tracheal wall.

### 3.2. Histopathologic and immunohistochemical findings

Macroscopically, the resected tracheal tumor consisted of a reddish hard nodule, measuring 3.5 × 3.3 × 2.5 cm, involving the bilateral bronchus. On the cut section, the tumor was solid with a gray-tan appearance extending into the surrounding adipose tissue of the trachea and bilateral bronchus and accompanying the stenosis of the tracheal wall.

Microscopic examination of the resected tracheal tumor demonstrated infiltrative growth from beneath the bronchial epithelium into the surrounding fatty tissue of the bronchial wall, which was composed of the 2 distinct carcinoma components. One component was a conventional low-grade ACC, as seen in the biopsy specimen, which consisted of a mixture of tubular and cribriform patterns (Fig. 2A). Both neoplastic epithelial and myoepithelial cells were bland and had uniform nuclei (Fig. 2A), and mitotic figures were rarely observed (<1/10 high-power fields). No solid nests were noted. In addition, perineural invasion was prominent (Fig. 2A, inset).

The other component was dedifferentiated carcinoma, which was composed of variable-sized and irregular-shaped nests that formed ill-defined glandular structures with or without central necrosis (Fig. 2B). Neoplastic cells were polygonal and had rich slightly eosinophilic cytoplasm and large oval nuclei with coarse chromatin and conspicuous nucleoli (Fig. 2C). Mitotic figures were frequently seen (34/10 high-power fields). These 2 components were almost sharply separated; however, a few residual low-grade ACC were present within the dedifferentiated carcinoma component (Fig. 2B). No lymph node metastases were present; however, invasion of dedifferentiated carcinoma components was observed in the fatty tissue around the lymph nodes.

The results of immunohistochemical studies are summarized in the Table. An α-smooth muscle actin–positive myoepithelial component was present in the conventional low-grade ACC, but it was not present in the dedifferentiated carcinoma component. Strong expression of nuclear p53 and membranous HER2/*neu* proteins was observed only in the