Biology of Adenoid Cystic Carcinoma of the Tracheobronchial Tree and Principles of Management

Donna E. Maziak, MDCM, MSc, FRCSC, FACS

KEYWORDS

• Adenoid cystic carcinoma • Tracheal tumors • Surgical resection

KEY POINTS

- Adenoid cystic carcinoma of the trachea is a rare tumor.
- The mainstay of treatment remains surgical resection, even in the presence of positive margins or metastatic disease.
- Long-term follow-up is required with patients presenting late and surviving with recurrent disease for years.

BIOLOGY OF ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma (ACC) of the airway is an uncommon malignant tumor, of salivary gland-type. It is the second most common primary malignant tracheal neoplasm after squamous cell carcinoma. Histologically, it originates from the submucosal glands and is composed of small round cells arranged in a cribriform manner, with larger paler cells forming clumps and pseudoacini. The clinical and pathologic features of ACC of the trachea were first reported in 1859 by Billroth.[1] It was previously referred to as a benign glandular neoplasm or adenoma but is now considered a low-grade bronchial carcinoma that is malignant, frequently locally invasive, and often late to metastasize.

Patients typically are middle-aged, with an equal preponderance of men and women. There are no studies that have found an association with smoking or excessive alcohol consumption. It is most often slow-growing and diagnosis is often delayed for 5 or more years. Symptoms vary according to location of the tumor in the airway. This tumor tends to be locally infiltrative between the tracheal rings, producing the so-called iceberg effect, with late metastasis. These tumors will bulge into the lumen and cause symptoms of tracheal obstruction and even hemoptysis. Patients most commonly present with dyspnea but may also have wheezing, cough, hemoptysis, and stridor. Often, early in the presentation, patients are misdiagnosed with asthma or bronchitis, and are mistreated.

In recent years, advances have been made in genetic mutation studies, such as microarray, fluorescent in situ hybridization, and microsatellite polymerase chain reaction. All have been performed in ACC for better understanding of its pathogenesis and potential biomarkers that may affect treatment and prognosis. Thus far, high levels of *ki-67* and p63 have strongly correlated with a decreased survival rate. Terminal deoxynucleotidyl transferase mediated dUTP nick end labelling (TUNEL), an assay for apoptosis rates (if high levels of staining), has correlated with increased incidence

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Surgical Oncology, Division of Thoracic Surgery, Ottawa Hospital–General Division, University of Ottawa, 501 Smyth Road 6NW-6364, Ottawa, Ontario K1H 8L6, Canada
E-mail address: dmaziak@ottawahospital.on.ca

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of metastasis, extracapsular spread, grade, and stage; thereby decreasing survival rates.[2] Some tumors have displayed a fused gene product of chromosomes 6 and 9, MYB-FIB gene, and this may hold the key transformation of normal healthy cells into ACC. Individuals with KIT expression, a mast cell growth factor receptor, have shown response to imatinib, a targeted chemotherapy.

PATHOLOGIC FEATURES OF ADENOID CYSTIC CARCINOMA

The tumor resembles those arising in the salivary glands. Its growth may be polypoid and sometimes annular, causing luminal obstruction. It is usually nonencapsulated, characteristically growing within the submucosal layer, thereby often appearing for some distance from the mucosal abnormality, which is often only the tip of the iceberg. Perineural and lymphatic spread is common. It is thought that the traditional tumor-node-metastasis (TNM) staging for malignancy cannot be applied to ACC because of its unique pathologic features.

There is a correlation between 3 histologic subtypes of these tumors and prognosis[3]:

1. Cribriform, the most common, has prominent pseudocysts surrounded by uniform basaloid cells with few cytoplasm and is arranged in well-defined nests of variable sizes. These have the best prognosis (**Figs. 1** and **2**).
2. Trabecular has basaloid cells arranged in nests surrounded by variable amounts of eosinophilic hyalinized stroma (**Fig. 3**).
3. Solid type has basaloid cells that aggregate without tubular or cystic formation; the tumor cells are larger with mitotic figures and comedonecrosis (**Fig. 4**). These have the poorest prognosis.

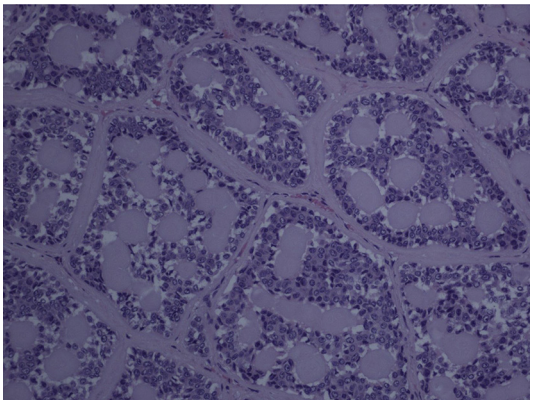

Fig. 1. ACC cribriform pattern hematoxylin-eosin (H&E) original magnification × 1 with islands and nests, with luminal matrix.

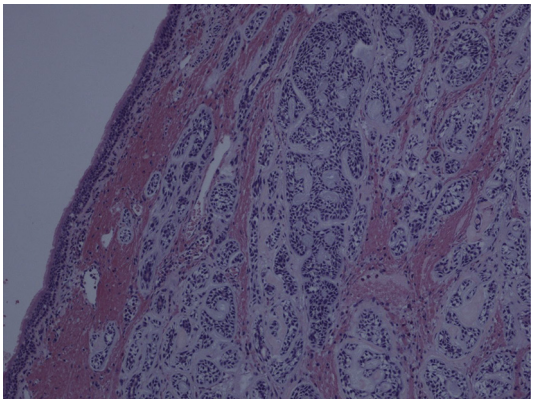

Fig. 2. ACC cribriform pattern subbronchial mucosa H&E original magnification × 1.

Usually, these patterns are mixed and pure patterns are very rare. The percentage of each pattern forms the basis of the grading system created in 1984 based on ACC in salivary glands.[4] From grades 1 to 3, there is a decreasing percentage of cribriform or tubular pattern (grade 1 has no solid component, grade 2 has <30% solid component) with an increasing percentage of solid component (grade 3 has >30% solid component).

Hematoxylin-eosin stain remains the gold standard by which the diagnosis is made; however, confusion with carcinoid or mucinous adenocarcinoma can occur. Further immunostaining may be required, including wide spectrum keratin, CK 7, actin, p63 and brain-derived neurotrophic factor.

PRINCIPLES OF MANAGEMENT

Diagnostic tissue biopsy by bronchoscopy and evaluation by an experienced pathologist is required given the orphan nature of this tumor. Further evaluation is required with computed

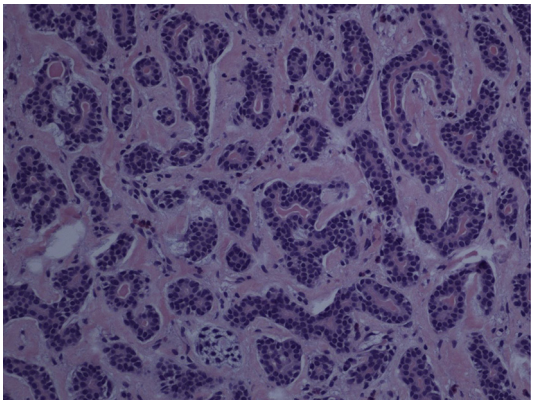

Fig. 3. ACC tubular pattern H&E original magnification × 1, with gland-like spaces.