Adenoid Cystic Carcinoma

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• Adenoid cystic carcinoma is a malignant tumor with a deceptively benign histologic appearance characterized by indolent, locally invasive growth with high propensity for local recurrence and distant metastasis. The tumor is composed of basaloid cells with small, angulated, and hyperchromatic nuclei and scant cytoplasm arranged into 3 prognostically significant patterns: cribriform, tubular, and solid. Some tumors undergo dedifferentiation into a high-grade form. Numerous studies have attempted to elucidate accurate histologic prognostic features but have often yielded conflicting results. Microarray analysis and gene expression profiling have provided new potential diagnostic and prognostic markers. However, tumor grade, stage, lymph node metastasis, invasion of major nerves, and margin status remain the most consistent predictors of prognosis. The combination of surgery and postoperative radiation therapy has improved locoregional control of the disease. Despite this achievement, late local recurrence and distant metastasis rates remain high and may occur decades after initial diagnosis.

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Overall, adenoid cystic carcinoma (ACC) is a rare tumor, accounting for only 1% of all malignant tumors of the oral and maxillofacial region. It accounts for 22% of all salivary gland malignancies and is one of the most common malignant tumors of the minor salivary and seromucinous glands. The most common site is the minor salivary glands of the oral cavity. However, involvement can occur in almost any site with a secretory gland component and has been reported in sites such as the lacrimal gland, breasts, uterine cervix, esophagus, lungs, and prostate.

First described in 1853, this neoplasm underwent numerous name changes before being given its current name by Spies in 1930. Adenoid cystic carcinoma is well known for its prolonged clinical course and tendency for delayed onset of distant metastases. The tumor has a well-described histologic appearance with certain features that may predict prognosis. Surgical removal is often difficult given the tumor’s propensity for invasion into adjacent structures and completely negative margins may not be attainable. Radical surgery has not been shown to improve survival or reduce local recurrence when compared with a conservative surgical approach and postoperative radiation. Currently, the prevention and prediction of late local and distant recurrence remains difficult and there is a lack of prospective randomized multicentric trials to guide optimal treatment and surveillance.

CLINICAL FEATURES

Adenoid cystic carcinoma is most common in the fifth and sixth decades of life. However, it can appear at virtually any age. The patient population in 1 recent review was reported to range from 10 to 96 years. Gender predication is an inconsistent feature in the literature with some authors reporting a male predominance and others finding a female or no gender predication. In decreasing order, the most common sites of ACC appear to be the minor salivary glands of the oral cavity, the major salivary glands, and the extraoral seromucinous glands. The clinical course is characterized by an initial period of slow and indolent growth that is usually asymptomatic. In most cases the tumor goes unnoticed until it has invaded local nerves and structures causing varying symptoms depending on location. Thus, most patients will present with locally invasive disease. In a recent review of ACC of the nasopharynx, 74.3% of patients showed advanced disease at the time of initial evaluation. Despite this, cervical lymph node metastasis is a rare event. Instead, the tumor spreads through a hematogenous route with distant metastasis appearing years, even decades, after initial diagnosis. In 1 recent series, rate of distant metastasis was reported as 47.8% with mean time to distant metastasis reported as approximately 5 years. Yet, the disease-free intervals in this study ranged from 8 to 150 months, highlighting the need for close long-term surveillance. The most common site of distant metastasis is the lung, followed by bone with other common sites including the liver and the brain. Unlike lung metastasis, the course of disease is usually fulminant if metastases occur in bone, especially the spine.

Most patients will undergo extensive resection followed by postoperative radiation regardless of margin status. With this treatment modality, disease-free survival rates at 5 years are generally high. Consistent use of postoperative radiation therapy has been associated with a local control rate of 95% at 5 years. Unfortunately, despite improved local control, disease-free survival rates decline significantly at 10 and 15 years. Additionally, recent series...
found no difference in survival, rate of recurrence, and time to recurrence between patients treated with surgery and postoperative radiation and those treated with surgery alone. Furthermore, distant and local recurrence can occur concurrently and despite initial local control, leading several authors to consider distant and local recurrence as separate diseases. Guidelines regarding management of metastatic disease are still not fully established. However, prolonged survival, even in the presence of multiple lung metastases, is not unusual. Fordice et al suggest that there may be 2 patient populations in ACC: One “doomed to rapid death from aggressive tumor” and another doomed to a prolonged course measured in decades.

GROSS PATHOLOGY

The tumor is typically a firm, poorly circumscribed, and unencapsulated mass. Tumor size typically averages from 1 to 8 cm in maximum dimension. Tumor size greater than 3 cm has been associated with increased rates of distant metastasis. The cut surface is white to gray-white with a solid appearance. Hemorrhage and necrosis are rare features and should raise the suspicion of high-grade transformation into dedifferentiated ACC.

HISTOPATHOLOGY

The microscopic appearance of the tumor is heterogeneous, consisting of varying amounts of 3 distinct growth patterns; however, the cytology of the tumor cells themselves is relatively uniform. The cells of the tumor display a basaloid appearance with angulated, hyperchromatic nuclei and scant, clear to eosinophilic cytoplasm. Electron microscopy and immunohistochemical analysis have shown that the tumor cells represent 2 populations of cells showing either myoepithelial or intercalated duct cell differentiation.

Three growth patterns for ACC have been described: cribriform, tubular, and solid. The cribriform subtype is the most frequent. It is composed of islands of basaloid cells surrounding variably sized cystlike spaces forming a “Swiss cheese” or sievelike pattern (Figure 1). The cystlike spaces are referred to as “pseudocysts” because they do not represent true glandular lumina and are contiguous with the surrounding stroma. The pseudocysts contain basophilic glycosaminoglycans and/or eosinophilic, periodic acid–Schiff–positive basal lamina material. Rare, true glandular lumina composed of cuboidal cells showing ductal differentiation can also be found scattered throughout and their presence greatly aids in diagnosis (Figure 2).

The tubular pattern shows similar cytology with the tumor cells arranged in nests surrounded by variable amounts of eosinophilic, often hyalinized stroma. Occasionally, the stroma component is increased, compressing the tumor cells into thin strands, forming a “trabecular” pattern. Well-formed ducts with recognizable inner epithelial and outer myoepithelial layers are more prominent than in the cribriform pattern. The continuity of the pseudocysts with the surrounding stroma is also more prominent.

The solid pattern contains aggregates of basaloid cells without tubular or cystic formation. Although the basaloid cytology of the tumor cells is retained, the tumor cells may be larger and nuclear pleomorphism may be more pronounced. Mitotic figures and comedonecrosis may also be seen. As in the cribriform pattern, true ducts will occasionally be seen scattered among the sheets of cells. This feature, along with accompanying areas of cribriform or tubular growth, can aid in differentiation from other basaloid neoplasms.

The percentages of each pattern form the basis of the grading system composed by Szanto et al. Grade I tumors contain only the tubular or cribriform growth pattern, grade II tumors contain cribriform or tubular growth with less than 30% solid component, and grade III tumors contain more than 30% solid component. Although the prognostic significance of this grading system has been questioned, the presence of a solid component has been a consistent predictor of poor prognosis in several series. However, a recent series of 23 patients with ACC found no statistically significant associations between histologic grade and local recurrence, distant metastasis, or overall survival. In addition, grading can be difficult as 1 tumor may show varying degrees of more than 1 subtype. Instead, several authors have reported that staging using the American Joint Committee on Cancer stage tumor stage is more predictive of prognosis and distant metastasis. Careful documentation of perineural invasion during staging is especially important as identification of invasion of major (ie, cranial) nerves has been shown to be of greater prognostic significance than minor nerve invasion.

High-grade or “dedifferentiated” ACC contains 2 histologic components: an area of conventional ACC of any grade and an area of high-grade undifferentiated carcinoma or poorly differentiated adenocarcinoma. The most common histologic appearance of the dedifferentiated component in 1 recent series was poorly differentiated cribriform adenocarcinoma. The high-grade areas do not display any histologic features of ACC and most importantly display loss of ductal-myoepithelial differentiation. Other findings include increased (>5 per high-power field) mitotic activity, comedonecrosis, micropapillary and squamoid growth patterns, and fibrocellular desmoplasia.

IMMUNOHISTOCHEMICAL FINDINGS

Use of immunohistochemical stains such as smooth muscle actin, S100, and smooth muscle myosin heavy chain will highlight cells showing myoepithelial differentiation surrounding the pseudocysts (Figure 3). The lumens of the pseudocysts will stain positively for basement membrane components such as type IV collagen and laminin. Adenoid cystic carcinoma of the salivary gland has also been shown to be strongly positive for c-KIT (CD117) regardless of grade. Strong c-KIT expression will be seen in almost all neoplastic cells in the solid pattern, all cells surrounding pseudocysts in the cribriform pattern, and all luminal cells in the tubular pattern (Figure 4).

Many markers have been studied as potential prognostic indicators in ACC. Increased expression of the cellular proliferation marker Ki-67 is seen with increasing amounts of solid (grade III) component and has been shown to correlate with worse prognosis. Thus, it may be a useful adjunct in assignment of tumor grade and prognosis. Ki-67 and p53 may show increased staining in areas of high-grade transformation. Increased p53 expression may also be an independent marker of poor prognosis.
MOLECULAR/ANCILLARY STUDIES

Past studies have shown that tumor aneuploidy correlates with more aggressive disease and a poor prognosis. A recent study of 52 cases of ACC showed that deletion of 1p-32-36 was the most common genetic change in ACC and was significantly associated with solid tumor phenotype and decreased overall survival. Because of the poor response of ACC to chemotherapy, newer studies have attempted to use molecular techniques to define potential future therapeutic targets. A recent large-scale microarray analysis of 15 cases of ACC found the transcription factor–encoding gene SOX4 was significantly overexpressed in ACC relative to normal salivary gland tissue. Genes encoding AP-2α and AP-2γ as well as genes highly involved in the Wnt/β-catenin signaling

Figure 1. Cribriform growth pattern displaying several prominent pseudocysts surrounded by basaloid cells with hyperchromatic angulated nuclei (hematoxylin-eosin, original magnification ×200).

Figure 2. High-power view displaying the characteristic eosinophilic basement membrane material in pseudocysts. Several true glands lined by cuboidal epithelium are visible in the center (hematoxylin-eosin, original magnification ×400).

Figure 3. Immunohistochemical stain for smooth muscle actin as a marker for myoepithelial differentiation (original magnification ×400).

Figure 4. Immunohistochemical stain for CD117 (c-KIT) showing strong staining around pseudocysts (original magnification ×400).
pathway were also overexpressed. The study also confirmed increased expression of genes indicative of myoepithelial differentiation as well as those involved in the production of basement membrane and extracellular matrix. As previously mentioned, ACC of the salivary gland has been shown to strongly express c-KIT. A recent study found multiple heterogeneous point mutations of the c-kit gene in 8 of 14 cases of ACC of the salivary gland. The application of these findings regarding therapeutic targets remains to be defined.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of ACC includes tumors that also exhibit tubular and cribriform structures such as polymorphous low-grade adenocarcinoma, tumors with basaloid cellular morphology such as basal cell adenoma and basal cell adenocarcinoma, and tumors with a dual population of ductal and myoepithelial cells such as pleomorphic adenoma.

Pleomorphic adenoma can be identified by the presence of mesenchymal, especially cartilaginous, differentiation in the stroma. The differential diagnosis may be more difficult on fine-needle aspiration biopsy, especially in cases of cellular pleomorphic adenoma with scant stroma. A recent study found that expression of glial fibrillary acidic protein and CD57 could be reliably used in cell block preparations to differentiate pleomorphic adenoma from ACC. In this study of 10 cases, 100% of cases diagnosed as pleomorphic adenoma expressed glial fibrillary acidic protein and 80% expressed CD57. None of the cases of ACC were positive for either marker. Basal cell adenoma can be identified by the presence of a capsule and lack of stromal and perineural invasion. Basal cell adenocarcinoma may be more difficult to differentiate with solid ACC; however, lack of clear cytoplasm and hyperchromatic, angulated nuclei with the presence of peripheral palisaded nuclei in the former may aid in diagnosis. Also, most tumors displaying a solid component of ACC will often display areas of cribriform or tubular growth.

Polymorphous low-grade adenocarcinoma occurs almost exclusively in the minor salivary glands and may contain overlapping histopathologic features with ACC such as ductal, tubular, and even cribriform growth. Perineural invasion is also common. However, the presence of cuboidal or columnar cells containing pale and ovoid nuclei with eosinophilic cytoplasm is in contrast with the hyperchromatic and angulated cells of ACC. In addition, polymorphous low-grade adenocarcinoma lacks a dual population of ductal and myoepithelial cells and typically has negative or low (less than 50% of cells) expression of c-KIT compared with the high c-KIT expression of ACC.

**CURRENT TREATMENT, COMMENT, AND RECOMMENDATIONS**

Optimal treatment of ACC has not yet been fully established. Although most authors advocate the use of surgical excision and postoperative radiotherapy, some series have found no statistically significant difference between patients treated with combination therapy and those treated with surgery alone. Careful tumor staging and grading with documentation of perineural invasion and margin status continue to be important prognostic tools. Additional prognostic information can be obtained using Ki-67 and p53 staining. There may be an increasing role for cytogenetic and gene expression analysis as additional prognostic factors. However, studies evaluating the efficacy of chemotherapeutic and molecular therapies remain disappointing. Close follow-up and surveillance of all patients for recurrence and metastasis is essential, although no formal guidelines exist regarding the most appropriate mode and duration of surveillance. Once metastatic disease has occurred, especially in the lungs, many patients can survive for long periods. Despite this, ACC is currently incurable and most patients will eventually succumb to local recurrence, distant metastasis, or both. The clinical course of the disease can be surprisingly heterogeneous with some patients surviving decades and others surviving only months. In 1 series, survival in patients with initial recurrence presenting as distant metastasis ranged from 5 months to 12½ years. Clearly more accurate measures of prognosis are needed, along with studies examining the use of molecular and genetic changes as therapeutic targets. Therefore, proper physical examination followed by surgery and radiation with close surveillance and careful attention to quality of life issues are the cornerstone of management of this disease.

**References**


