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Review

Adenoid cystic carcinoma of the head and neck – An update ☆

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SUMMARY

This article provides an update on the current understanding of adenoid cystic carcinoma of the head and neck, including a review of its epidemiology, clinical behavior, pathology, molecular biology, diagnostic workup, treatment and prognosis. Adenoid cystic carcinoma is an uncommon salivary gland tumor that may arise in a wide variety of anatomical sites in the head and neck, often with an advanced stage at diagnosis. The clinical course is characterized by very late recurrences; consequently, clinical follow-up should extend at least >15 years. The optimal treatment is generally considered to be surgery with postoperative radiotherapy to optimize local disease control. Much effort has been invested into understanding the tumor's molecular biological processes, aiming to identify patients at high risk of recurrence, in hopes that they could benefit from other, still unproven treatment modalities such as chemotherapy or biological therapy.

Introduction

With a reported yearly incidence of 3–4.5 cases per million [1], adenoid cystic carcinoma (AdCC) is an uncommon tumor, accounting for about 1% of all head and neck malignancies [2] and about 10% of all tumors of the salivary glands [3]. It is the most commonly reported malignant tumor of the minor salivary glands (MSGs) [1] and is also one of the most common cancers of the major salivary glands (the parotid, submandibular and sublingual salivary glands) [4]. AdCC can also involve lacrimal and ceruminous glands as well as other sites in the head and neck, including the nasal and paranasal sinuses, trachea and larynx [1,6–10].

AdCC was first described by Robin, Lorain and Laboulbene in two articles published in 1853 and 1854 reporting on one parotid and two nasal tumors. These authors described the characteristic cribriform arrangement of tumor cells on microscopy and noted the invasion of surrounding structures and the spread along nerves [11]. In 1856, Billroth suggested the term "cylindroma" for this tumor; the current name of "adenoid cystic carcinoma" was introduced by Spies in 1930. Despite the initial observations of Robin et al. the tumor was regarded as a variant of the benign mixed tumor. The malignant nature of this tumor was finally established by Dockerty and Mayo [12].

AdCC is a relentlessly growing tumor characterized by perineural invasion and multiple local recurrences. Regional lymph node metastases are conventionally regarded as rare, but these may be under-recognized due to potentially occult, clinically undetectable

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cervical metastases, infrequent neck dissections for this tumor and arguably a lack of detailed pathological assessment of lymph nodes. In sharp contrast, hematogenous metastasis is common, especially to lung, bone and liver [11,13].

Clinically, AdCC is regarded a high-grade neoplasm, and consequently the treatment of choice is radical surgical resection and is almost always followed by postoperative radiotherapy [1,14]. Chemotherapy (both cytotoxic chemotherapy and targeted molecular therapies) has been extensively studied in patients with advanced AdCC, but the rather indolent course of the disease makes it difficult to observe clinical responses [15].

In the setting of incurable AdCC, the benefits and risks of treatment should be carefully weighed, as palliative chemotherapy for this often indolent malignancy may be associated with toxicity without known impact in disease course and patient prognosis [16]. Therefore, some asymptomatic patients with incurable disease may be observed without treatment, sometimes for years; chemotherapy is generally recommended when patients have demonstrated rapidly progressive disease or are symptomatic [17].

Epidemiology

AdCC is most frequently found in the parotid, submandibular and MSGs. A large Danish population-based study estimates that AdCC accounts for 27.9% of the overall incidence of salivary gland cancers (SGCs) (11/1,000,000/year), corresponding to an annual incidence of 3/1,000,000/year [1]. In Nova Scotia, the annual incidence raises to 4.5/1,000,000 cases [18]. It is important to note that these incidence estimates are certainly affected by challenges of histological diagnosis of SGCs, with reclassification rates ranging from 14% to 29% in several studies [1,19,20]. The cribriform pattern is easily recognized, but other patterns may be less familiar to non-specialists; epidemiological studies of SGCs should therefore consider the center from which the data has been collected.

The proportion of AdCC among SGCs varies according to the site/location of the primary tumor. In a Dutch nationwide study of parotid carcinoma, AdCC was the most frequent histology, accounting for 1 out of every 6 parotid cancers [21]. The likelihood of AdCC is even greater in the submandibular gland, where it accounts for 40% of SGCs [4,22]. AdCC is the most common cancer in MSGs, where the proportion of AdCC ranges from 32% to 71%. In MSGs, AdCC is most commonly found in the palate, followed by the paranasal sinuses (14–17%) and other sites of the oral cavity [10,23].

The tumor occurs in all age groups with a high frequency in middle-aged and older patients [24], the 5th and 6th decades being most commonly affected [1,11,20,25–27]. There are no distinct risk factors, and smoking is not known to affect the incidence [28].

Clinical behavior

AdCC has been described as having an apparently indolent course; however, it has an aggressive long-term behavior, with persistent and recurrent growth pattern and late onset of metastases resulting in frequent eventual death [25]. It has been described as "one of the most biologically destructive and unpredictable tumors of the head and neck" [29].

The most common presenting symptom is a slowly growing mass, followed by pain attributed to its tendency for perineural invasion. The association between pain, facial nerve dysfunction and microscopic perineural invasion was emphasized in a Netherlands' Cancer Institute cohort of patients with parotid carcinoma, where the majority of patients with these features had AdCC [30]. In the study of Nascimento et al. [24], 98% of patients reported a mass, 48% had pain, 30% had ulceration, and one patient had facial nerve paralysis; these symptoms had been present from 1 month to 4 years. The presenting symptoms of AdCC vary according to the site of disease. In major salivary glands the tumor produces a mass, and when located in the parotid, facial nerve palsy may occur; in the palate a mass is common, though ulceration or even oro-antral fistula may be seen; in the larynx dyspnea could be the first presenting symptom; in the nose and paranasal sinuses, nasal obstruction, deep facial pain, epistaxis and eye symptoms are at the forefront [5,10,31].

Pathology and diagnosis

On routinely-prepared histological sections of resection specimens examined with the naked eye and at scanning magnifications, AdCCs are asymmetrical tumors, with variously lobulated or invasive growth patterns (Fig. 1).

Morphologically, AdCC largely consists of non-luminal, basaloid, hematoxyphilic cells, with small to moderate amounts of cytoplasm, and far fewer luminal, short cuboidal, eosinophilic cells (Figs. 2 and 3A). The nuclei tend to be relatively bland with small or inconspicuous nucleoli. The luminal cells may be inconspicuous, though immunohistochemical markers assist in their distinction (Fig. 3B).

Three distinct architectural patterns have been described: *tubular* (usually bilayered tubules lined by luminal cells surrounded by non-luminal cells that often show "clear" cytoplasm); *cribriform* [basaloid cells arranged in variable sized, oval/rounded masses punched-out by rigid, oval, cyst-like spaces (pseudolumina) that may contain "cylinders"/globules of hyaline material and/or myxoid glycosaminoglycans, and occasional small true lumina lined by luminal cells]; and *solid* (largely basaloid tumor cells growing in sheets without lumina formation) (Fig. 2) [32,33].

AdCC is traditionally regarded as originating from the intercalated duct region – hence comprising a population of duct-like and purportedly myoepithelial-like cells [34]. Clearly, the luminal cells show duct-like phenotypes. Caution should be exerted before characterizing the basaloid cells as either neoplastic or modified myoepithelia. Smooth muscle actin (SMA) immunoreactivity has been described in AdCCs [35], but combined electron microscopy and stereology showed that typical myoepithelial cells are rare (3% of the tumor-cell population) [36]. Observations with special stains or immunohistochemical markers should also be carefully interpreted (Fig. 4).

Classic AdCC often shows a combination of cribriform and tubular patterns. In most studies, a solid growth pattern is associated with worse prognosis, advanced stage and development of distant metastases [30]. Szanto et al. [37] proposed a histologic grading scheme for AdCCs based on the degree of solid pattern. Three grades were suggested: Grade I, tumors with tubular and cribriform areas, but without solid components; Grade II, cribriform tumors that were purely or mixed with >30% of solid areas; and Grade III, tumors with a predominantly solid pattern.

Neural invasion can be seen even in early-stage tumors and has been regarded as an unfavorable prognostic factor, associated with distant metastasis and adverse final outcome (Figs. 1C, 2C, and 5) [26,38]. Recently, however, an analysis of 495 AdCCs from 9 international patient cohorts indicated that "while perineural invasion has no impact on survival, intraneural invasion is an independent predictor of poor prognosis" [39]. Another inference was that neural invasion did not predict hematogenous spread; distant metastases were related to age, primary site and nodal (N) classification. Teymoortash et al. [40] reviewed 22 cases of AdCC with documented perineural invasion and proposed a new classification scheme for AdCCs based on the presence of characteristic features in perineural invasion. They classified tumors as p1 when true perineural or endoneural invasion was observed (Fig. 5) and