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REVIEW

Cervical Lymph Node Metastasis in High-Grade Transformation of Head and Neck Adenoid Cystic Carcinoma: A Collective International Review

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ABSTRACT

Adenoid cystic carcinoma (AdCC) is among the most common malignant tumors of the salivary glands. It is characterized by a prolonged clinical course, with frequent local recurrences, late onset of metastases and fatal outcome. High-grade transformation (HGT) is an uncommon phenomenon among salivary carcinomas and is associated with increased tumor aggressiveness. In AdCC with high-grade transformation (AdCC–HGT), the clinical course deviates from the natural history of AdCC. It tends to be accelerated, with a high propensity for lymph node metastasis. In order to shed light on this rare event and, in particular, on treatment implications, we undertook this review: searching for all published cases of AdCC-HGT. We conclude

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that it is mandatory to perform elective neck dissection in patients with AdCC-HGT, due to the high risk of lymph node metastases associated with transformation.

Keywords: Adenoid cystic carcinoma; Dedifferentiation; Fatal outcome; Local recurrence; High-grade transformation; Lymphatic metastasis; Neck dissection; Neoplasm recurrence; Salivary glands

REVIEW

The concept of high-grade transformation (previously also termed dedifferentiation) in neoplasms was introduced in 1971. Dahlin and Beabout [1] described a distinct entity in which a low grade chondrosarcoma was associated with a histologically high-grade sarcoma. High-grade transformation (HGT) in salivary gland tumors is rare but has been described not only in adenoid cystic carcinoma (AdCC) but in acinic cell carcinoma (AcCC) [2–7], polymorphous low-grade adenocarcinoma [8–10], epithelial-myoepithelial carcinoma [11–14], low-grade mucoepidermoid carcinoma [15], myoepithelial carcinoma [16], hyalinizing clear cell carcinoma [17, 18], and mammary analogue secretory carcinoma (MASC) [19, 20]. The molecular genetic mechanisms responsible for these transformations remain largely unknown but a few genes have been documented in HGT of salivary gland neoplasms, such as *P53* gene mutation and *C-MYC* amplification [21–24]. HGT in salivary tumors of low-grade malignancy, such as AcCC, is associated with a higher local recurrence rate, a higher propensity for local lymph node metastasis and, a dramatic worsening of prognosis. For example, AcCC has the best prognosis of all salivary malignancies (10-year survival ~90%), but HGT in AcCC significantly reduces the mean survival of patients to 4.3 years [5, 25].

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HGT in AdCC (AdCC-HGT) was first described in 1999 by Cheuk et al. [26] as "dedifferentiated adenoid cystic carcinoma" and since then more than 40 cases have been reported in the literature, most of them involving sinonasal and palatal minor glands and the submandibular glands [21, 23, 26–42]. AdCC-HGT is histologically characterized by a residual component of conventional AdCC and another distinct anaplastic cell population showing loss of the biphasic ductal and myoepithelial differentiation seen in conventional AdCC. HGT in AdCC may be apparent at the time of primary excision of the tumor or may develop in a recurrence [26]. The two components may be separate, but transitional zones can be recognized. The presence of a transitional zone may help to distinguish AdCC-HGT from a hybrid tumor in which one of the two components is an AdCC. It may also be that many of the hybrid tumors [43] reported in the literature represent HGT in different salivary tumors. The distinction between the solid type of AdCC and AdCC-HGT should be emphasized. The histological criteria distinguishing between the two have been outlined in 2007 by Seethala et al. [33]. The solid type of AdCC is known to have the worst prognosis of the different histological subtypes of conventional AdCCs. Distant metastasis developed in 73% of major salivary gland solid type AdCC compared to 8% and 17% in cribriform and tubular types, respectively [44]. Most reports indicate that the prognosis for patients with AdCC-HGT is even worse than for those with a solid type of AdCC [24, 33, 36] and thus its recognition is important for the individual patient. The cells in the solid type of AdCC have small hyperchromatic nuclei and a basaloid appearance; the transformed cells in AdCC-HGT have larger and more pleomorphic, vesicular nuclei. The

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tubular-cribriform component of AdCC retains some of the myoepithelial immunoprofile. The conventional AdCC component in AdCC-HGT can have any mixture of growth patterns, with predominance of the cribriform and tubular patterns. The HGT component, which usually is either a poorly differentiated adenocarcinoma, or less often, an undifferentiated carcinoma, shows cells with large pleomorphic nuclei and a high mitotic rate (Fig. 1). The nuclei contain vesicular chromatin with conspicuous nucleoli. Necrosis (including comedonecrosis) is common as is a desmoplastic stroma and, tumoral calcification. Squamous areas and micropapillary growth are unique patterns seen exclusively in AdCC-HGT as compared to conventional AdCC [33]. There is an altered immunoprofile detected as a loss of the abluminal layer of myoepithelial cells [e.g. p63 and other myoepithelial/basal cell markers such as calponin, smooth muscle actin (SMA) and smooth muscle myosin heavy chain (SMMHC)], although there may be S-100 protein expression. Ki-67 (often more than 50%) and p53 labeling indices are often elevated while CD117 is generally lost. In some cases, cyclin D1 overexpression, as well as p53 abnormalities in association with Her-2/neu overexpression or loss of pRb expression, have all been detected in the AdCC-HGT component [21, 26, 30]. Studies by Seethala et al. [24] have shown *C-MYC* amplification in the process of HGT in AdCCs

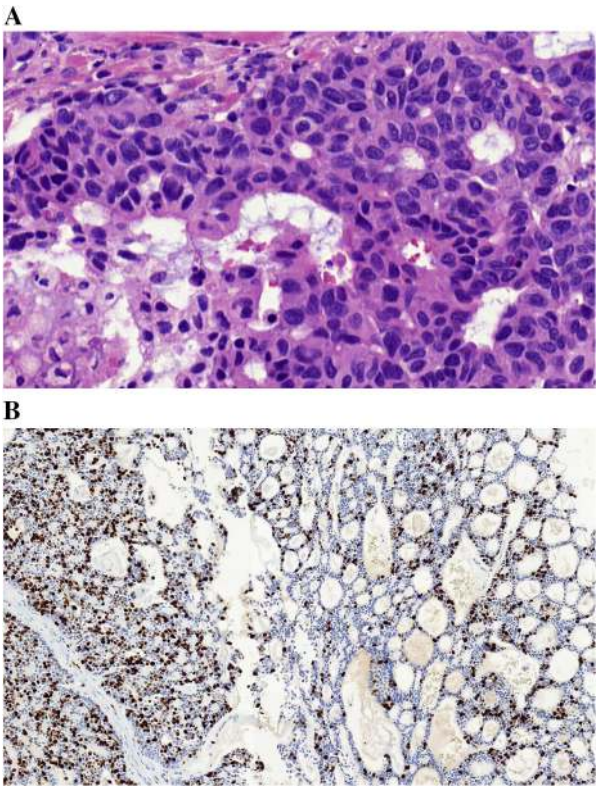

Fig. 1 High-grade transformation in adenoid cystic carcinoma (AdCC-HGT). **a** The transformed AdCC consists of sheets of atypical, cells and loss of architecture usually seen in a conventional AdCC. **b** AdCC-HGT with a very high labeling index with Ki-67 (*left*) and a much more modest Ki-67 index in the remnants of the conventional AdCC (*right*)

while other oncogenes, more frequently on chromosome 17q23, are also present, warranting further investigation. Recently, Costa et al. [45] studied 8 cases of AdCC-HGT and demonstrated that *MYB*/*NFIB* translocation is not necessarily an early event in or fundamental for the progression into AdCC-HGT.

There are statements that AdCC-HGT has a high propensity for lymph node metastasis, with as many as 57% of the patients showing metastatic disease compared to 5–25% of patients with conventional AdCC (cribriform, tubular and solid patterns) [33, 46]. The risk for nodal disease in AdCC-HGT is likely to be

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distinctly higher when compared to conventional AdCC as many lymph nodes in cases of conventional AdCC are involved by direct extension from the primary tumor rather by a true metastasis as identified in our review of 44 cases of AdCC-HGT reported in the literature (Table 1) [21, 23, 26–42, 45, 47]. Kusafuka et al. [48] described a case of early transformation only and therefore was not included. Taking into account the possibility that some or even many of the reported hybrid tumors may represent HGT in different tumors, the number of AdCC-HGT could be even higher. Of the approximately 35 cases of hybrid tumors reviewed by Hellquist and Skalova [49], AdCC was the most common malignancy and was seen in 18 of the 33 malignant cases: two hybrid tumors comprised benign components only, and all but one of the remainder had two malignant components. The present review revealed cervical lymph node metastasis in 12 of 29 cases of AdCC-HGT. In 17 additional cases, the authors clearly stated there was no metastasis, while the remaining 15 reports did not include information about lymph node status. Thus, for the 29 cases in which information about lymph node metastasis (present or absent) was given, positive nodes were reported in 41% (12/29). In six cases with cervical lymph node metastasis distant metastases were also reported (50%). However synchronous or metachronous presentation could not be assessed in this review (Table 1). Seethala et al. [33] described 11 cases of AdCC-HGT where 4 of the 11 cases (36%) had cervical lymph node metastases with multiple positive nodes and extracapsular extension in all four cases (5 positive nodes of 29, 2/2, 3/18 and 2/22), a percentage similar to the literature review.

In the study from the MD Anderson Cancer Center of 60 patients with early-stage (pT1, pT2) AdCC of conventional type, seven of the 30 patients who received neck dissection had occult metastasis (23%). This study primarily aimed to evaluate the risk for distant metastasis and survival rather than development of criteria for neck node dissection, but nevertheless, 43% of patients who had positive cervical lymph nodes after neck dissection developed distant metastasis compared to 17% who did not have positive nodes or a neck dissection. This study also demonstrated that 73% of patients with the solid subtype of conventional AdCC developed distant metastasis compared to 8% and 17% for cribriform and tubular subtypes, respectively. The subtype of AdCC among the seven patients who developed nodal disease was not specifically stated [44].

The concept of HGT in AdCC was widely accepted after the publication of Cheuk et al. [26] in 1999. There is, however, an uncertain number of reports of AdCC prior to that date, which today, according to the histological description, very likely would have been classified as AdCC-HGT. As an example, the 1985 report by Stillwagon et al. [50] would fit as AdCC-HGT: “Histologically, the tumor was an adenoid cystic carcinoma with cribriform and solid areas as well as some areas of undifferentiated carcinoma”. For obvious reasons, it is impossible to review all single case reports of AdCC in the literature to document possible cases of AdCC-HGT and, therefore, only cases classified as AdCC-HGT or dedifferentiated AdCC, published after 1999 have been included in this review and are summarized in Table 1. The current review of AdCC-HGT emphatically demonstrates the importance of a very generous sampling of the surgical specimens as the HGT component may be very small. In fact, ideally the entire tumor should be sectioned and examined whenever possible. Not only will careful dissection and

Table 1 Review of reported cases of adenoid cystic carcinoma with high-grade transformation

Authors (year) [references]	No. of cases	Age	Location	Cervical lymph node metastasis	Distant metastasis	Remarks (gender, tumor size, status, follow-up)
Cheuk et al. (1999) [26]	3	55	Tongue	Present	Bone, lung	F, NA, DOD, 15 months
		53	Soft palate	Absent	Lung	F, NA, DOD, 9 months
		38	Hard palate	Present	Absent	M, NA, DOD, 18 months
Moles et al. (1999) [27]	1	61	Tongue	NA	NA	M, 3 cm, NED, 60 months
Terasaki et al. (2000) [28]	1	49	Lacrimal gland	NA	NA	F, NA, NA, NA
Chau et al. (2001) [21]	1	64	L submandibular gland	Present	NA	F, 3 cm, NED, 6 months
Ide et al. (2003) [29]	1	62	Soft palate	NA	NA	M, 2.2 cm, NA, NA
Nagao et al. (2003) [30]	6	55	L maxillary sinus	Present	Bone, lung	F, 6.0 cm, DOD, 6 months
		51	R submandibular gland	Absent	Bone	M, 4.5 cm, DOD, 24 months
		35	L nasal cavity	Absent	Absent	F, 1.8 cm, DOD, 36 months
		70	R submandibular gland	Present	Absent	M, 3.5 cm, DOD, 69 months
		34	R maxillary sinus	Present	Absent	F, NA, AWD, 60 months
		36	L nasal cavity	Absent	Bone, lung	M, 1.7 cm, DOD, NA
Brackrock et al. (2005) [31]	1	NA	NA	NA	NA	HGT first after radiotherapy
Sato et al. (2006) [32]	1	74	R maxillary sinus	Absent	Lung, liver, spleen, bone, pulmonaryhilar lymph nodes	M, 4 cm, DOD, 4 months

Table 1 continued

Authors (year) [references]	No. of cases	Age	Location	Cervical lymph node metastasis	Distant metastasis	Remarks (gender, tumor size, status, follow-up)
Seethala et al. (2007) [33]	11	72	R maxillary sinus	NA	NA	M, NA, NA, NA
		59	Pterygopalatine	Absent	Absent	M, NA, DOD, 12 months
		57	R submandibular	Present	Lung	M, 7 cm, DOD, 15 months
		53	L nasal	Absent	Lung	F, 4 cm, DOD, 12 months
		62	R submandibular	Present	NA	F, 1.7 cm, Alive, 48 months
		61	R paranasal sinus	NA	NA	F, NA, Dead, 44 months
		66	R pyriform	Absent	NA	M, 7 cm, Dead, 8 months
		32	Maxillary	Present	NA	M, 6 cm, NA, NA
		64	R palate	Absent	NA	F, 2.7 cm, AWD, 1 month
		42	R submandibular	Present	Soft tissue	M, 3 cm, AWD, 3 months
		66	R submandibular	Absent	Absent	M, 2 cm, Alive, 2 months
Handra-Luca et al. (2009) [34]	1	51	Maxillary sinus	NA	Lung	F, NA, NA, NA
Malhotra et al. (2009) [35]	1	54	R parotid	NA	Absent	M, 5 cm, NED, 5 months
Bonfitto et al. (2010) [23]	7	44	Submandibular	Absent	Absent	F, T2, NA, 18 months
		55	Palate	Absent	Absent	F, T4, NED, 140 months
		65	Paranasal sinus	Absent	Absent	M, T4, Dead, 8 months
		49	Parotid	Absent	Liver	F, T3, Alive, 33 months
		64	Submandibular	Present	Liver	F, T2, DOD, 7 months
		58	Lips	Absent	Absent	F, T2, NED, 18 months
		47	Palate	Present[a]	Lung	M, T4, Alive, 12 months

Table 1 continued

Authors (year) [references]	No. of cases	Age	Location	Cervical lymph node metastasis	Distant metastasis	Remarks (gender, tumor size, status, follow-up)
Costa et al. (2011)[b] [36]	1	61	Paranasal sinus	NA	Absent	F, T2, Alive, 144 months
Panarelli et al. (2011) [37]	1	52	Lacrimal gland	NA	NA	M, 3.2 cm, AWD, 12 months
Boland et al. (2012) [38]	3	61	Parotid	NA	NA	F, NA, Alive, 169 months
		56	Parotid	NA	NA	M, NA, ANED, 77 months
		40	Submandibular	NA	NA	M, NA, ANED, 6 months
Argyris et al. (2013) [39]	1	39	Lacrimal gland	NA	NA	F, 3 cm, AWD, 24 months
Bayle et al. (2013) [40]	1	45	Palate	NA	NA	F, 4.5 cm, NA, NA
Ly et al. (2013) [41]	1	88	Parotid	Absent	Absent	F, 3 cm, Alive, 12 months
Sayar et al. (2013) [42]	1	39	L submandibular gland	Absent	NA	F, 4.0 cm, NED, 36 months
Total Data Available	44	54.4	2 Tongue	17 Absent	13 Absent	
			7 Palate	12 Present	13 Present	
			3 Lacrimal gland	15 NA	18 NA	
			11 Submandibular			
			9 Paranasal sinus			
			3 Nasal cavity			
			5 Parotid			
			3 Other			
			1 NA			

Alive alive (no further information), *ANED* alive with no evidence of disease, *AWD* alive with disease, *Dead* dead (no further information), *DOD* dead of disease, *F* female, *HGT* high-grade transformation, *L* left, *M* male, *NA* information not available, *NED* no evidence of disease, *No* number, *R* right

[a] A later study by Costa et al. in 2012 [47] and another one in 2014 [45] comprised 8 cases; 7 of the cases derived from the 2010 study by Bonfitto et al. [23] and the additional 8th case from the 2011 study by Costa et al. [36]. In the 2014 study by Costa et al. [45], it is stated that this same particular palatal tumor did not have any cervical lymph node metastasis

[b] In the 2011 study, Costa et al. [36] reported 6 cases of AdCC-HGT, however, 5 of the cases were included in the previous 2010 study by Bonfitto et al. [23]; hence only one new case presented in this 2011 study by Costa et al. [36]

histologic evaluation help to identify any possible focus of HGT, but may also highlight areas of solid subtype in a conventional AdCC.

CONCLUSION

Based on the literature review, lymph node metastasis may occur in 43–57% of patients with AdCC-HGT. This high propensity for lymph node metastases, which is at least 5–10 times higher than for conventional AdCC, strongly supports the use of neck dissection for patients with this unique histology. Preoperative staging workup is mandatory due to the high risk of distant metastasis. In situations where such histology is not recognized until after extirpative surgery for the primary, it appears justified to subsequently include the neck electively in the post-operative radiotherapy or perform a postoperative elective neck dissection (if distant metastasis are ruled out) followed by adjuvant radiation therapy to the primary site and the regional lymph nodes.

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