

# “Dedifferentiation” and High-Grade Transformation in Salivary Gland Carcinomas

Toshitaka Nagao

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**Abstract** “Dedifferentiation” and/or high-grade transformation (HGT) has been described in a variety of salivary gland carcinomas, including acinic cell carcinoma, adenoid cystic carcinoma, epithelial-myoeplithelial carcinoma, polymorphous low-grade adenocarcinoma, myoeplithelial carcinoma, low-grade mucoepidermoid carcinoma and hyalinizing clear cell carcinoma, although the phenomenon is a rare event. Recent authors tend to preferably use the term HGT instead of “dedifferentiation” in these cases. HGT-tumors are composed of conventional carcinomas juxtaposed with areas of HG morphology, usually either poorly differentiated adenocarcinoma or “undifferentiated” carcinoma, in which the original line of differentiation is no longer evident. The HG component is generally composed of solid nests, sometimes occurring in cribriform pattern of anaplastic cells with large vesicular pleomorphic nuclei, prominent nucleoli and abundant cytoplasm. Frequent mitoses and extensive necrosis is evident. The Ki-67 labeling index is consistently higher in the HG component. p53 abnormalities have been demonstrated in the transformed component in a few examples, but the frequency varies by the histologic type. HER-2/*neu* overexpression and/or gene amplification is considerably exceptional. The molecular-genetic mechanisms responsible for the pathway of HGT in salivary gland carcinomas largely still remain to be elucidated. Salivary gland carcinomas with HGT have been shown to be more aggressive than conventional carcinomas with a poorer prognosis, accompanied by higher local recurrence rate and propensity for cervical lymph node

metastasis, suggesting the need for wider resection and neck dissection.

**Keywords** Salivary gland · Pathology · Dedifferentiation · High-grade transformation · Acinic cell carcinoma · Adenoid cystic carcinoma

## Introduction

In 1971, Dahlin and Beabout introduced the term “dedifferentiated chondrosarcoma” to describe a distinct clinicopathologic entity in which low-grade (LG) chondrosarcoma was associated with—but sharply delineated from—histologically dissimilar high-grade (HG) sarcoma [1]. Subsequently, “dedifferentiation” has become a well-known phenomenon in bone and soft tissue tumor pathology [2]. After the first report of a “dedifferentiated” salivary gland acinic cell carcinoma (AcCC) in 1988 [3], several investigators described this phenomenon not only in AcCC [4–15], but also in other salivary carcinomas such as adenoid cystic carcinoma (AdCC) [16–27], epithelial-myoeplithelial carcinoma (EMC) [28–42], polymorphous low-grade adenocarcinoma (PLGA) [43–46], myoeplithelial carcinoma [47], LG mucoepidermoid carcinoma (MEC) [48, 49] and hyalinizing clear cell carcinoma (HCCC) [50, 51], all of which undergo “dedifferentiation” or high-grade transformation (HGT). Therefore, the concept of this development is now established for salivary gland neoplasms [52].

“Dedifferentiation” is defined as the abrupt transformation of a well-differentiated tumor into HG morphology that lacks the original distinct histologic characteristics. The conventional and HG carcinomatous areas are clearly demarcated, although a transitional zone can be identified in some cases. The HG tumor element is characterized by

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T. Nagao (✉)  
Department of Anatomic Pathology, Tokyo Medical University,  
6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan  
e-mail: nagao-t@tokyo-med.ac.jp

pleomorphism, prominent necrosis and a high cell proliferation rate, as assessed by mitotic count and Ki-67 labeling index (LI). “Dedifferentiated” components are commonly reported to be either poorly differentiated adenocarcinomas or “undifferentiated” carcinomas. In the literature “dedifferentiated” salivary gland carcinomas have sometimes been confused with hybrid carcinomas, which are composed of two distinct tumors entities [32], but they should be distinguished from each other from a clinicopathological point of view.

As for salivary gland pathology, recent authors often tend to use the term HGT instead of “dedifferentiation” in these cases. In salivary gland carcinomas, unlike bone and soft tissue tumors, recognition of loss of the original line of differentiation is frequently not clearly distinct, especially when HG adenocarcinomas arise in conventional gland-forming carcinomas, e.g., AcCC, AdCC, EMC and PLGA. Therefore, the term HGT is preferred and may more accurately represent such phenomena [12, 21, 36].

The development and progression of malignant tumors is regulated by the expression and genetic and/or epigenetic alterations of various oncogenes and tumor suppressor genes. Although the data are limited, involvement of one or several genes has been documented in the HGT process of salivary gland tumors. While the presence of a transitional zone between conventional and HG carcinoma components suggests an identical origin and is considered to indicate progression of malignancy, it remains unsettled whether the process of HGT represents a failure of differentiation in stem cells or whether differentiated neoplastic cells undergo “dedifferentiation.”

This review evaluates the clinicopathological characteristics, including immunohistochemical and molecular-genetic findings, of “dedifferentiation” and/or HGT in salivary gland carcinomas reported thus far and describes these characteristics with respect to each tumor type.

#### Acinic Cell Carcinoma

AcCC is a low grade malignant epithelial neoplasm of the salivary glands in which at least some of the neoplastic cells demonstrate serous acinar differentiation characterized by the presence of cytoplasmic zymogen secretory granules [53]. This type of tumor accounts for approximately 4 % of all salivary gland tumors and between 7 and 17.5 % of malignant salivary neoplasms [54, 55].

Since the first cases of AcCC with “dedifferentiation” were reported by Stanley et al. [3], slightly less than 50 such cases have been described in the literature [4–15]. Although HGT is considered to be a rare event in AcCC, Chiosea et al. [15] recently found that 11 of 71 AcCCs (15.5 %), including 36 of their consultation cases,

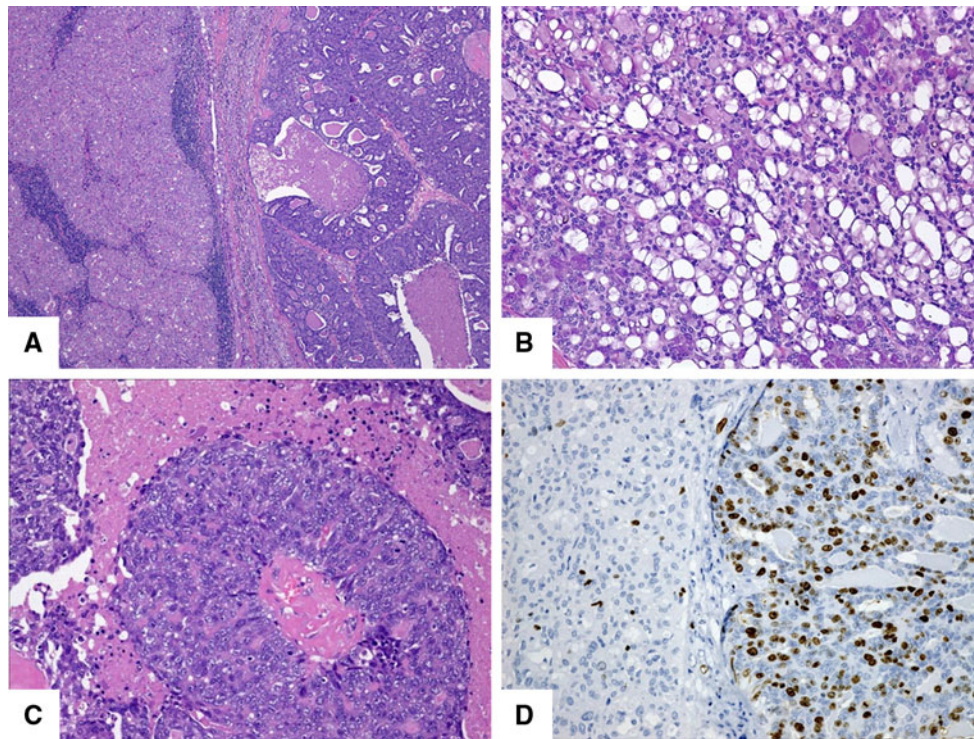
exhibited HGT. The parotid gland was affected in all reported AcCC cases with HGT. The mean age of 61–66 years observed in patients with HGT-AcCC is approximately 20 years higher than that of patients with conventional AcCC [12, 15]. HGT-AcCC presents with a slight female predominance, similar to that of conventional AcCC.

HGT-AcCCs are composed of conventional low grade (LG) AcCCs juxtaposed with areas of HG tumors; this component is usually either “undifferentiated” carcinoma or poorly differentiated adenocarcinoma (Fig. 1a) with no significant intermixing or transition between the two. HG foci may be identified in the initial primary tumor; however, there are reports of patients with prior surgery for conventional AcCC in some reported cases. The conventional LG AcCC component generally exhibits solid and/or microcystic growth of a unifying feature of small to medium-sized tumor cells (Fig. 1b), sometimes accompanied by lymphoid stroma. Mitotic figures are scanty. Diastase-resistant PAS-positive cytoplasmic granules are evident at least focally. In contrast, the HG component is generally composed of solid nests (Fig. 1c), sometimes occurring in cribriform pattern, of anaplastic cells with large vesicular pleomorphic nuclei, prominent nucleoli and abundant cytoplasm. These cells fail to exhibit any features of acinar differentiation. There are frequent mitoses and a central comedo-type of necrosis. Vascular and perineural invasion is common. Metastatic foci are comprised of both LG and HG components in most cases.

According to the immunohistochemical studies reported in the literature, especially those documented by Skálová et al. [12], all but one [9] HGT-AcCCs are devoid of the myoepithelial phenotype and none showed immunoexpression for the androgen receptor or 3+ positivity for HER2/*neu*. All nine cases analyzed showed strong membrane staining for  $\beta$ -catenin in the HG component, whereas staining in the LG areas was mildly cytoplasmic and nuclear. The median cyclin-D1 index is higher in the HG component than in the LG AcCC. p53 overexpression is uncommon, even in HG areas. Ki-67 LI is always higher in the HG component (Fig. 1d).

Some authors have demonstrated the presence of an aneuploid DNA content in the HG component of the tumor, in contrast to that observed in conventional AcCC, which is diploid [4, 7]. No alterations of the *TP53* gene have been found thus far [6, 7, 12]. FISH analyses do not demonstrate gene amplification of HER2/*neu* in any of the transformed areas [12].

As expected, HGT-AcCCs behave in a more aggressive manner and are associated with poorer clinical outcomes (mean overall survival: approximately 4 years), a higher local recurrence rate and a higher propensity for lymph



**Fig. 1** High-grade transformation of acinic cell carcinoma. **a** Low-power view of the biphasic histology of the tumor comprising a high-grade carcinoma with solid and cribriform patterns of growth and comedonecrosis (*right portion*), and a conventional acinic cell carcinoma with a lymphoid stroma (*left portion*). The two components are sharply separated from each other. **b** Conventional acinic cell carcinoma showing microcystic and focal solid growth of tumor

cells of a unifying nuclear feature. Mixture of basophilic acinar-type cells is evident. **c** High-grade carcinoma exhibiting solid patterns of growth with extensive necrosis. Carcinoma cells contain large vesicular pleomorphic nuclei and prominent nucleoli. Several mitoses are also observed. **d** High-grade carcinoma displays a high Ki67 labeling index (*right portion*), in contrast to a low index in conventional acinic cell carcinoma (*left portion*)

node metastasis (50 %) as well as distant metastases than conventional AcCC [12, 15].

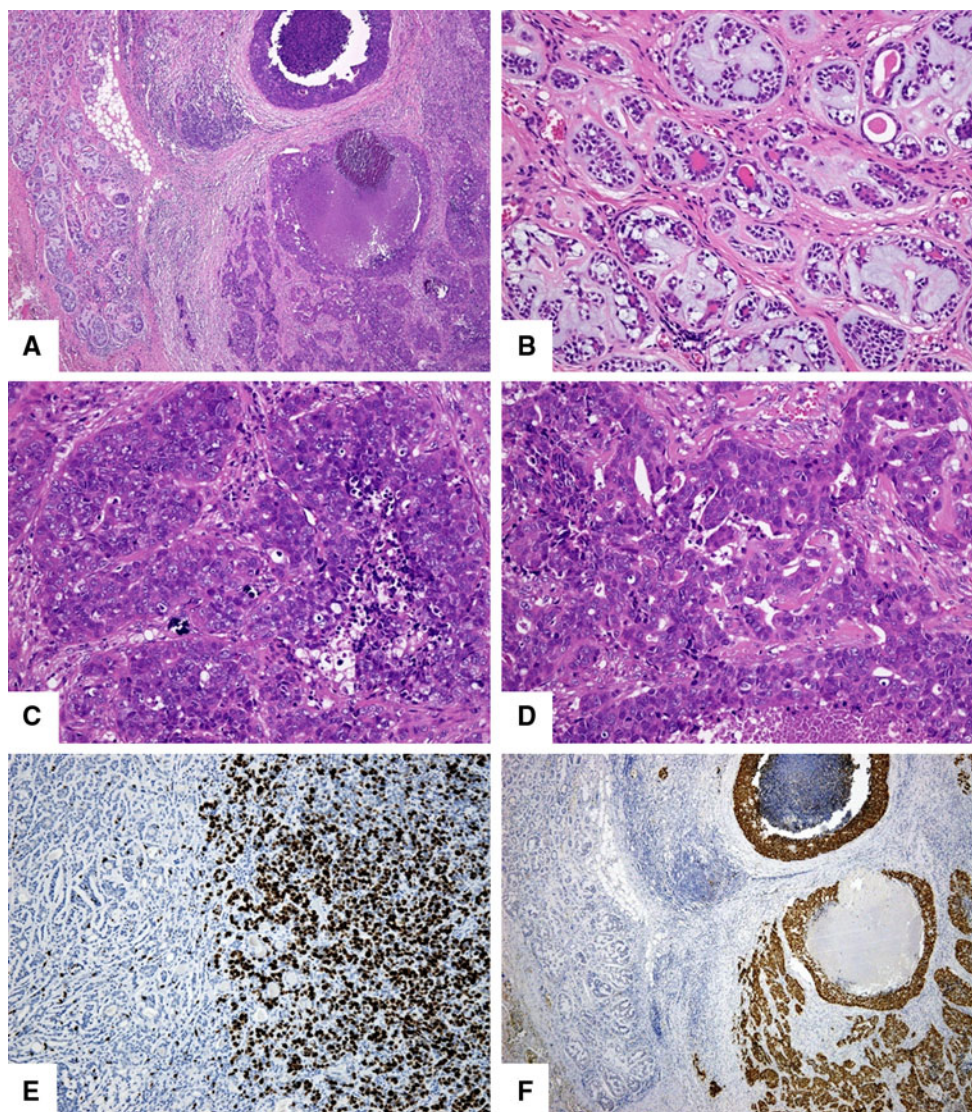
#### Adenoid Cystic Carcinoma

AdCCs are common malignancies arising in major and minor salivary glands, including the seromucinous glands of the upper respiratory tract and the lacrimal glands. AdCCs are characterized clinically by an indolent course, a relatively high rate of local recurrence and late onset of distant metastases. Histologically, AdCCs may exhibit a mixture of three distinctive growth patterns: cribriform, tubular, and solid. The predominant growth pattern is predictive to some extent of the clinical outcome. AdCCs with both tubular and cribriform patterns generally have better prognoses than those with the solid pattern.

Since the first documentation of “dedifferentiated” AdCC presented by Cheuk et al. [16], a total of approximately 40 cases with “dedifferentiated” or HGT AdCC have been recognized in the literature to date [16–27]. Three cases of hybrid carcinoma composed of AdCC and salivary duct carcinoma have been reported, but from our review of the literature, they may represent additional

examples of HGT-AdCC [56–58]. The tumors preferentially develop in the intraoral minor salivary glands and seromucinous glands of the upper respiratory tract; however, a small number of cases also occur in the submandibular, parotid and lacrimal glands. HGT-AdCC primarily affects older adults in the sixth decade of life or later, with a slight male predominance. Although a few previously reported cases of HGT-AdCC have developed in recurrent tumor sites following radiotherapy, the majority of cases are diagnosed at initial presentation.

HGT-AdCC contains two distinct carcinomatous components: conventional AdCC of any growth pattern, and HG carcinoma with a loss of the histologic features characteristic of AdCC, *e.g.*, biphasic ductal and myoepithelial differentiation (Fig. 2a). The conventional AdCC and HG carcinoma components are generally clearly separated from each other; however, in some cases, a transitional zone is recognized between them. The proportion of each carcinoma in a tumor mass varies from case to case. The conventional neoplasm consists primarily of a mixture of cribriform and tubular patterns (Fig. 2b). Solid cell nests may also be seen. The cribriform pattern includes pseudocysts containing PAS- and alcian blue-positive basal



**Fig. 2** High-grade transformation of adenoid cystic carcinoma. **a** Low-power view showing two distinct carcinomatous components: conventional adenoid cystic carcinoma (*left portion*) and high-grade carcinoma with a predominantly solid growth pattern, forming irregular and confluent tumor nests (*right portion*). Comedo-like necrosis is evident in the high-grade component. **b** Conventional adenoid cystic carcinoma exhibiting cribriform pattern with excessive extracellular basal lamina material and two cell-layered tubular structures. The tumor cell nuclei have a bland, uniform appearance.

**c** and **d** High-grade carcinoma component. Solid (**c**) and micropapillary (**d**) growth patterns of carcinoma cells exhibiting large pleomorphic nuclei with a moderate amount of cytoplasm. Note prominent necrosis. **e** Ki-67 labeling index of the high-grade carcinoma component (*right portion*) is much higher than that of the conventional adenoid cystic carcinoma component (*left portion*). **f** Only high-grade carcinoma on the right is strongly and diffusely positive for p53

lamina material. Scattered small, true glandular structures are also observed. The tubular structures have an inner layer of duct-lining cells and an outer layer of clear cells. The more frequent cell type contains small, angular dark nucleus with scant cytoplasm, while the other type includes a duct-like cuboidal cells. The nuclei in the conventional component exhibit a bland, relatively uniform appearance without pleomorphism, and mitotic figures are rare. In comparison, the HG carcinoma, which is a predominant element, is usually either poorly differentiated

adenocarcinoma (Fig. 2c, d) or less commonly “undifferentiated” carcinoma. Poorly differentiated adenocarcinoma displays a predominantly solid growth pattern (Fig. 2c), forming irregular and confluent tumor nests with a few tubular structures, often creating cribriform architecture. Micropapillary features may be present focally (Fig. 2d) [21]. A trabecular pattern within the fibrous stroma can be also seen. Some cases may histologically show moderately differentiated adenocarcinoma [24, 52]. “Undifferentiated” carcinoma is characterized by solid cell nests with

streaming and scattered small squamous eddy-like whorls [19, 21]. Necrosis is commonly seen, and sometimes central comedo-like necrosis superficially resembling salivary duct carcinoma is identified. Microcalcifications may be seen, usually in areas of necrosis. The HG carcinoma cells exhibit large pleomorphic nuclei with a moderate amount of cytoplasm and high mitotic activity. These tumor nuclei contain vesicular chromatin with conspicuous nucleoli. Lymphovascular invasion is frequently observed. The metastatic lesions of lymph nodes usually harbor only HG carcinoma.

Before the diagnosis of HGT-AdCC is made, the solid-type AdCC should be excluded carefully [19, 21]. Similar to the HGT-AdCC component, cellular atypia, occasional comedo-like necrosis, and frequent mitotic figures may be seen in the solid-type AdCC. In the solid-type AdCC, however, solid cell nests are commonly intermixed with cribriform and tubular structures throughout the tumor, instead of being clearly separated from them as in HGT-AdCC. Also, the cytologic details help to distinguish the two entities. The cells of the solid-type AdCC have a basaloid feature characterized by small, densely hyperchromatic, and monotonous appearing nuclei with scanty cytoplasm. In contrast, transformed carcinoma cells have larger, more pleomorphic and vesicular nuclei with a moderate N/C ratio. Furthermore, the solid-type AdCC may retain focal myoepithelial differentiation.

Immunohistochemical analyses reveal consistent loss of myoepithelial markers, as demonstrated by the lack of  $\alpha$ -smooth muscle actin, calponin and p63 staining in the HG component. Ki-67 LI is much higher in the transformed components compared with that observed in conventional AdCC (Fig. 2e). Approximately half of reported cases show p53 staining of a large percentage of tumor cells restricted in the HG areas (Fig. 2f), suggesting that p53 abnormalities play a major role in the development of HGT-AdCC [16, 18–21]. Unlike salivary duct carcinoma, androgen receptors are always negative. Diffuse and strong membranous HER2/*neu*-positivity is identified restricted to the HG component in a few cases [19, 20]. A loss of the pRb expression occurred in only a single case, in which the patient was negative for p53 and HER-2/*neu* [19]. C-kit is positive in both conventional and HG populations and does not help in discriminating between the two components [21]. Increased immunoexpression of GLUT1, a key molecule regulating the transport and metabolism of glucose, and mitochondrial antigen has been reported in the HG component [24, 59]. However, a more recent paper indicated no significant alterations in the levels of the expression of HIF-1 $\alpha$  relating to hypoxia, VEGF and CD105 during the process of HGT in AdCC [59].

A high-resolution microarray comparative genomic hybridization (CGH) analysis revealed a correlation between

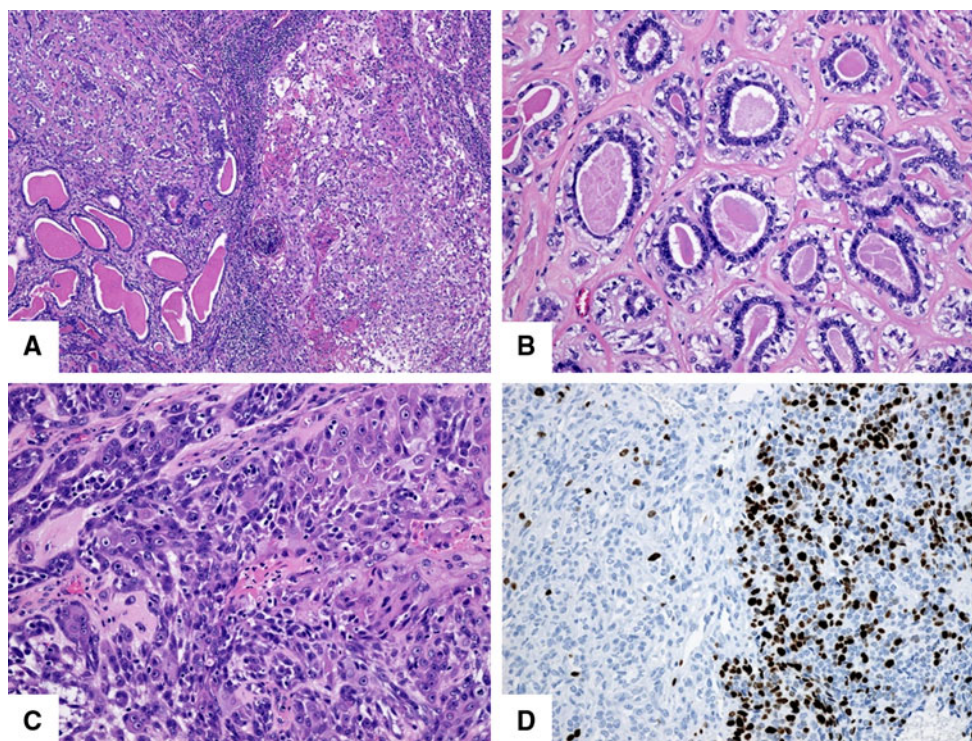
the number of chromosomal aberrations and the degree of gland differentiation of the transformed component [60]. FISH analyses have demonstrated increases in *MYC* and low-level increases in *ERBB2*, formerly known as *HER2/neu*, in cases showing gains on array CGH in these regions [61]. It has recently been reported that the *MYB-NFIB* fusion gene generated by a recurrent t(6;9) translocation is identified in a significant subset of AdCCs [62–64]. The detection of this fusion gene may be helpful in the diagnosis of the HGT-AdCC, although this has not yet been demonstrated.

Similar to other salivary gland carcinoma types, HGT-AdCC is a highly aggressive tumor with a strong tendency to recur and metastasize to the lymph nodes and distant organs. Metastasis to lymph nodes is frequent, occurring in 57 % of patients versus 5–25 % of patients with conventional AdCC [21]. The latter may also include lymph nodes involved by direct extension from the primary tumor. The median survival in 24 reported patients was 36 months, which is similar to that of solid-type AdCC however in 11 cases of HG-AdCC reported by Seethala et al. [21], the median survival was estimated to be 12 months, thus suggesting that HGT-AdCC follows a more aggressive course than solid-type AdCC.

#### Epithelial-Myoepithelial Carcinoma

EMC is an uncommon neoplasm, accounting for approximately 1 % of all salivary gland tumors [53–55]. Histologically, it is characterized by a malignant tumor composed of variable proportions of two cell types that typically form duct-like structures. The biphasic morphology is represented by an inner layer of duct-lining, epithelial-type cells and an outer layer of clear, myoepithelial-type cells. EMC is considered to be an LG malignancy with rare mortality.

EMC containing a HG component has been described under various terms, including “HG carcinoma component in EMC,” [29] “dedifferentiated EMC,” [30, 33, 34, 37, 42] “EMC with/of HGT,” [35, 36, 40, 41] “aggressive EMC” [39] and “EMC with myoepithelial anaplasia” [33, 38]. Abrupt transition of the myoepithelial and/or ductal component of EMC into HG carcinoma is referred to as “dedifferentiated EMC” (Fig. 3a), whereas “myoepithelial anaplasia” is defined by Seethala et al. [33] as a gradual transition of the myoepithelial component of EMC into a more aggressive carcinoma. A literature review revealed that a total of 22 such cases have been reported [28–42]. The average age of the patients (72 years) is higher than that of conventional EMC patients (60 years) [36]. Similar to conventional EMC, HGT-EMC most often involves the parotid gland followed by the submandibular gland.



**Fig. 3** High-grade transformation of epithelial-myoeplithelial carcinoma. **a** Two distinct carcinomatous components: epithelial-myoeplithelial carcinoma (*left portion*) and high-grade carcinoma (*right portion*), are evident. **b** Conventional epithelial-myoeplithelial carcinoma exhibits biphasic ductal structures, comprising inner

eosinophilic cells and outer clear cells of minimal atypia. **c** High-grade carcinoma is composed of pleomorphic tumor cells with prominent nucleoli. There is focal squamous differentiation. **d** Higher Ki-67 labeling index is noted in the high-grade carcinoma component (*right portion*)

Histologically, the HG component frequently exhibits solid growth of tumor cells with greater cytological atypia, higher mitotic frequency and extensive areas of necrosis (sometimes similar to comedo-necrosis) and lacks the features of biphasic duct-like structures characteristic of conventional EMC (Fig. 3b, c). Bizarre tumor cells may also be occasionally observed. A spindle, clear and plasmacytoid morphology, suggestive of myoeplithelial differentiation and squamous differentiation can be seen (Fig. 3c) [32, 33, 36]. In one recent case, the HG areas exhibited dual ductal and myoeplithelial differentiation, manifesting morphologically as salivary duct carcinoma and areas of myoeplithelial carcinoma [42]. In contrast to HGT-AdCC, which is consistently devoid of myoeplithelial differentiation in the transformed areas, most HG components of EMC preferentially exhibit a myoeplithelial nature rather than a ductal origin, although the immunohistochemical evidence may sometimes be limited [36]. Ki-67 LI is consistently higher in the HG component (Fig. 3d). One case was described in which the HG area was diffusely positive for p53 protein and cyclin D1 but negative for HER-2/*neu* overexpression [34]. Another case showed aberrant expression of prostate-specific antigen in the HG component [37].

HGT-EMC has been shown to be more aggressive than conventional EMC with a poorer prognosis (a reported survival of 1–72 months in HGT-EMC versus an average disease-free survival of 11.34 years in conventional EMC), accompanied by frequent extraglandular extension and a high propensity for lymph node (50 %) and distant (30 %) metastasis [36].

#### Polymorphous Low-Grade Adenocarcinoma

PLGA is defined as a malignant epithelial tumor characterized by architectural diversity, cytologic uniformity, an infiltrative growth pattern and a low metastatic potential [53]. It is the second most common type of malignant neoplasm of the minor salivary glands after MEC; however, it is exceedingly rare in the major glands.

There are six cases of PLGA with transformation to a higher histologic grade reported in the literature [43–46]. In three cases, HGT arising from typical PLGA developed after a protracted clinical course with recurrences treated with excision and radiation therapy. Five tumors arose in the palate [43, 45, 46], with the rest originating in the nasal cavity [44]. These tumors were composed of two distinct elements partly admixed with each other. One was

comprised of a variety of growth patterns, i.e., solid, cribriform, small tubules, fascicular streams, and occasional foci of Indian filing and micropapillary structures of small- to intermediate-sized, uniform and bland tumor cells. Mitoses were scant and no necrosis was found. These features were consistent with those of PLGA. Conversely, the other component considered to be poorly differentiated adenocarcinoma or “undifferentiated” carcinoma exhibited an HG morphology characterized by a predominantly solid and cystic growth pattern, nuclear atypia with prominent nucleoli, foci of necrosis, and high mitotic count. Ki-67 LI was increased tenfold in the latter compared to that observed in the former [46]. In one case, the HG element displayed androgen receptor positivity, thus resembling salivary duct carcinoma [46].

All reported PLGA patients with HGT did not develop distant metastases or died of their tumors, although all had extensive local disease and/or cervical lymph node metastases. However, there are too few reported cases to assess any distant metastatic potential.

### Myoepithelial Carcinoma

Myoepithelial carcinoma, also referred to as malignant myoepithelioma, is a rare salivary gland tumor that is the malignant counterpart of myoepithelioma. This tumor is defined as a neoplasm composed almost exclusively of tumor cells exhibiting myoepithelial differentiation, characterized by infiltrative growth and the potential for metastasis [53]. The morphological appearance of the tumor exhibits a very wide variation of histological and cytological types and a broad spectrum of grade, ranging from low to high [54, 55]. Although myoepithelial carcinoma is generally considered to be of intermediate to HG malignancy, its clinical behavior varies.

One case of “dedifferentiation” of LG myoepithelial carcinoma was reported by Ogawa et al. [47]. A 59-year-old male developed a parotid gland tumor composed of two distinct and separate neoplastic cell populations with no significant intermixing of tumor cells. The first population was diagnosed as LG myoepithelial carcinoma, occupying more than 80 % of the tumor, comprised of solid nests of polygonal eosinophilic or glycogen-rich clear cells displaying neoplastic myoepithelial morphological and immunohistochemical features. Although no cellular or nuclear pleomorphism was obvious, focal necrosis and occasional mitotic figures were observed. In contrast, the second population, regarded to be “undifferentiated” carcinoma, was composed of polygonal and short spindle cells with obvious pleomorphism and atypical mitoses. Immunohistochemistry revealed no evidence of myoepithelial differentiation, and positivity for p53 and cyclin D1 was noted in the second element only. The PCNA LI of the first

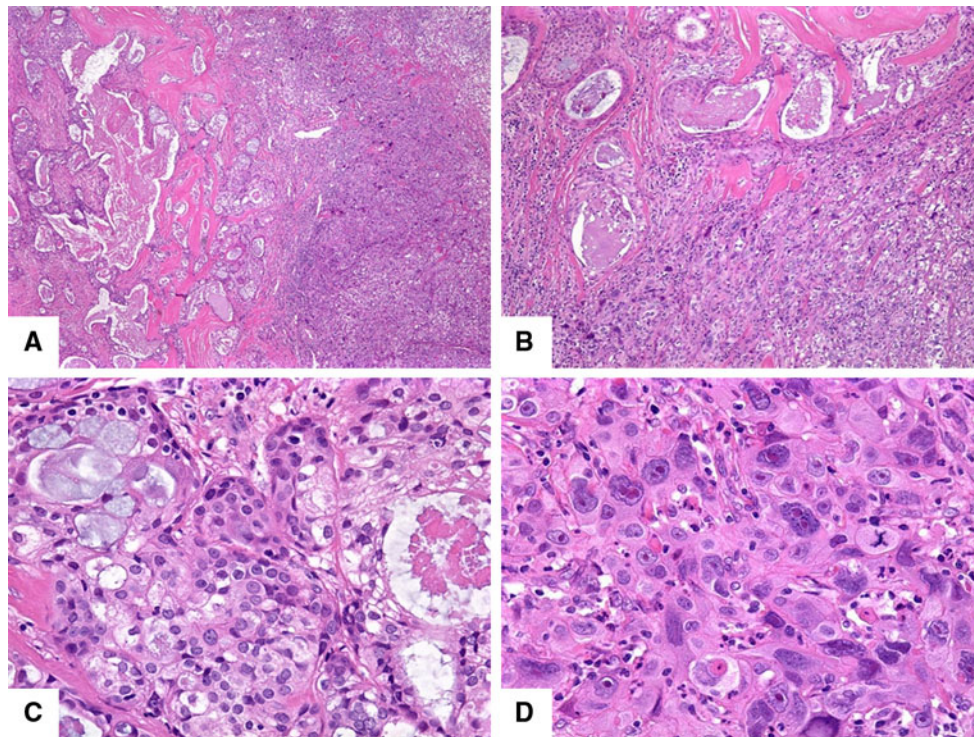
and second populations was 10 and 60 %, respectively. Although additional radiation therapy was administered, a rapidly growing recurrent growth was found at the primary site five months later. The recurrent tumor was excised together with the muscle, periosteum and skin. A second recurrence of the tumor was confirmed four months later. No metastasis was recognized. The recurrent tumor exhibited features of “undifferentiated” carcinoma composed of anaplastic spindle cells growing in a fascicular arrangement.

### Low-Grade Mucoepidermoid Carcinoma

MEC, one of the most common malignant salivary gland neoplasms, is divided into low-, intermediate-, and high-grade types according to the histologic features.

“Dedifferentiation” is extremely rare in MEC, with only two examples having been described [48, 49]. In 2003, we reported the first case involving a 55-year-old male with a parotid gland tumor [48]. Although the patient was alive 10 years after the initial diagnosis, the tumor recurred twice, once at three months and once at seven months after the initial resection. The second case involved a bronchial tumor in an 11-year-old girl that resulted in death within three months from the initial diagnosis accompanied by rapid metastases to the pleura, mediastinal lymph nodes, abdominal wall and vertebral bones [49].

Histologically, the tumors contained two distinct carcinomatous components, comprising a predominant HG anaplastic “undifferentiated” carcinoma and a minority LG MEC (Fig. 4a). Although both components were clearly separated from each other, a mixture of the two types of carcinoma formed an intervening transitional zone (Fig. 4b). The LG MEC component was characterized by multiple cystic structures with glandular formation and small, solid cell nests consisting of intermediate and mucous cells and a few epidermoid cells (Fig. 4c). The nuclei of these cells were uniformly bland, and mitotic figures were extremely rare. Necrosis was absent in the LG component. In comparison, the HG component consisted of solid and sheet-like growth patterns without any glandular or cystic structures (Fig. 4d). Focally, sarcomatoid growth features were also observed. Extensive necrosis was seen in the HG component. The carcinoma cells exhibited large pleomorphic nuclei with conspicuous nucleoli and a high mitotic rate. Mucous and squamous cells were absent. The HG element was completely devoid of the distinctive features of MEC. Rarely, foci of an LG neoplasm are present within an HG MEC, suggesting that the latter element develops through tumor progression. In such instances, however, a few mucous cells should be detected, even in the HG MEC component.



**Fig. 4** High-grade transformation of low-grade mucoepidermoid carcinoma. **a** Low-power view showing a low-grade mucoepidermoid carcinoma component composed mainly of cystic structures (*left portion*) and a high-grade anaplastic carcinoma component with a solid and sheet-like growth pattern (*right portion*). Note that the two components are sharply separated from each other. **b** The low-grade mucoepidermoid carcinoma component consisting of cystic and

glandular formations (*left upper portion*) and the solid growth of the high-grade anaplastic carcinoma component (*right lower portion*) are intimately connected. **c** Low-grade mucoepidermoid carcinoma component showing a mixture of intermediate, mucous goblet, and epidermoid cells. Note the bland appearance of the tumor cell nuclei. **d** High-grade carcinoma component showing solid growth of markedly pleomorphic tumor cells with prominent nucleoli

In the reported cases, immunoperoxidation of carcinoembryonic antigen expression was restricted to the LG MEC portion [48]. The Ki-67 LI was higher in the “dedifferentiated” component than in the LG component. In the first case, an image cytometric analysis revealed that the LG and HG carcinomas were diploid and aneuploid, respectively [48]. In addition, the second case involved *TP53* gene mutations and corresponding protein overexpression [49]. Since the *CRTC1* (also known as *MECT-1*)-*MAML2* fusion gene is considered to be a highly specific diagnostic marker for MEC [65–68], the identification of the fusion gene may be useful for the diagnosis of the “dedifferentiated” MEC. Although loss of the *CDKN2A* tumor suppressor gene has been described in the HG MEC as a candidate poor prognostic marker [66, 68], future studies will be needed to determine whether the gene alteration is involved in the development of “dedifferentiation” in MEC.

#### Hyalinizing Clear Cell Carcinoma

HCCC is a rare, LG salivary gland neoplasm that is characterized by bland infiltrating clear cells forming nests and cords within a hyalinizing stroma [69, 70]. HCCC exhibits

a consistent *EWSR1* rearrangement on FISH analyses as a result of the *EWSR1-ATF1* fusion oncogene [71].

Two suggestive examples of HGT-HCCC, both arising in the base of the tongue, have been described in the literature [50, 51]. The first case involved a 57-year-old female who presented with a tumor exhibiting the presence of minor foci of high mitotic frequency, necrosis and anaplasia within an otherwise typical LG HCCC [50]. The tumor was designated as an “aggressive variant” of HCCC. Widespread metastases and death occurred within one year of the initial presentation. The second case involved a 61-year-old male with HGT-HCC [51]. On the initial biopsy, sheets of clear and eosinophilic cells with a background of a myxoid-like matrix in addition to large, bizarre malignant cells, focal necrosis, and atypical mitotic figures were identified. The tumor was diagnosed as poorly differentiated carcinoma, not otherwise specified. More typical features of HCCC with rearrangement of the *EWSR1* gene were revealed in a FISH analysis in the recurrent tumor at follow-up 10 months after radiation therapy. On a re-staging workup, the patient was confirmed to have local disease with pulmonary metastases.



## Conclusion

“Dedifferentiation” and/or HGT are rare events in salivary gland carcinomas, and the descriptions of this phenomenon are few. Recent authors tend to preferably use the term HGT instead of “dedifferentiation” in such cases. This type of carcinoma is associated with an aggressive clinical behavior and a poor prognosis despite the histological types of the original tumor. The high propensity for cervical lymph node metastasis suggests the need to include neck dissection in the therapy. HGT of salivary gland carcinoma can occur either at initial presentation or less commonly at the time of recurrence, sometimes following the administration of postoperative radiotherapy. In practice, the potential for HGT in almost any type of salivary gland carcinoma warrants thorough sampling of all salivary gland tumors to prevent oversight of a component of HGT. Although p53 abnormalities have been demonstrated in the transformed component in a few examples, the molecular-genetic changes involved in the pathway of HGT in salivary gland carcinomas largely remain to be elucidated and require further studies to delineate their roles.

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