Salivary Duct Carcinoma of the Parotid Gland Originating from an Epithelial-Myoepithelial Carcinoma: Report of a rare case

Yuichiro Hamamoto[1] • Hiroshi Harada[1,2] • Motoyuki Suzuki[3] • Takashi Fujii[4] • Shin-ichi Nakatsuka[1]

[1]Department of Diagnostic Pathology and Cytology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka, Osaka 541-8567, Japan.

[2]Department of Diagnostic Pathology, Seichokai Fuchu Hospital, 1-10-17, Hiko-Town, Izumi-City, Osaka 594-0076, Japan.

[3]Department of Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan.

[4]Department of Head and Neck Surgery, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka, Osaka 541-8567, Japan.

Yuichiro Hamamoto, MD
E-mail: kyokui090088@gmail.com

Hiroshi Harada, DDS, PhD
E-mail: harapppiii@kzd.biglobe.ne.jp

Motoyuki Suzuki, MD, PhD
E-mail: msuzuki@ent.med.osaka-u.ac.jp

Takashi Fujii, MD, PhD
E-mail: fujii-ta@mc.pref.osaka.jp

Shin-ichi Nakatsuka, MD, PhD (Corresponding author)
E-mail: nakatuka-si@mc.pref.osaka.jp
Tel: +81-6-6945-1181, Fax: +81-6-6945-1900
E-mail: nakatuka-si@mc.pref.osaka.jp

Manuscript type: Case report

Total number of each:
1) text pages; 11
2) tables; 2
3) figures; 13

Acknowledgements
The authors thank all medical technologists (Osaka International Cancer Institute) for their technical assistance and Editage (www.editage.jp) for English language editing.
No funding obtained.

No conflict of interest to disclose.

The paper was not invited.

The precis: We presented a rare case with hybrid tumor of epithelial-myoepithelial carcinoma and salivary duct carcinoma. Our case could be considered as a dedifferentiated carcinoma as well as a hybrid tumor.

The anatomic site: parotid gland

Keywords: Salivary duct carcinoma・Parotid gland・Epithelial-myoepithelial carcinoma・ Dedifferentiation

Abstract

Salivary duct carcinoma (SDC) is a high-grade carcinoma with poor prognosis, especially among various salivary carcinomas. In this study, we report a rare case of SDC of the parotid gland originating from an epithelial-myoepithelial carcinoma (EMC). A 71-year-old Japanese man presented with swelling of the right parotid region and a right facial nerve paralysis for 10 months. He underwent extended total parotidectomy and chemoradiotherapy after the surgery. Histologically, a major part of the tumor was an androgen receptor (AR)-positive, human epidermal growth factor receptor 2 (HER2)- positive, gross cystic disease fluid protein-15 (GCDFP-15)-positive SDC, with a focus of a typical EMC component at the periphery of the lesion. In the transitional area of the two components, inner ductal cells of double-layered ducts showed similar morphology and immunophenotype to SDC. These findings suggest that SDC originated from the inner ductal cells of EMC. Because the tumor included an EMC as a low-grade carcinoma and an SDC as a high-grade carcinoma, we can consider our case as a dedifferentiated carcinoma as well as a hybrid tumor.

Introduction

Salivary duct carcinoma (SDC) is a high-grade malignancy of the salivary gland with poor prognosis, and it typically occurs in the parotid glands of elderly men [1]. Histologically, SDC resembles high-grade ductal carcinoma that primarily develops in the mammary gland. It is characterized microscopically by intraductal tumor island with papillary, cribriform, or solid configurations of cells with central comedonecrosis. Apocrine-like features, including decapitation secretion, large nucleus with swollen nucleoli, and eosinophilic cytoplasm, are often prominent in well-differentiated cases that are mainly composed of large and small ducts and cribriform structures. Moreover, scirrhous carcinoma-like histology is sometimes observed in poorly differentiated cases. SDC often arises from pleomorphic adenoma (PA) (carcinoma ex PA) and also develops *de novo*. Several case reports have described SDC with other distinct histology, such as acinic cell carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma (EMC), as a hybrid tumor [2-6]. Here, we report a rare case of primary SDC of the parotid gland originating from an EMC, which could be considered as a dedifferentiated carcinoma and a hybrid tumor.

Case report

Clinical summary

A 71-year-old Japanese man presented with swelling of the right parotid region and a right facial nerve paralysis for 10 months. Eighteen years before, he had undergone surgery for a right parotid tumor. The pathological diagnosis was PA. There was no significant past medical history besides hypertension, hyperlipidemia, and inguinal hernia. His family history was unremarkable. A physical examination revealed a fixed tumor in the right parotid region and swelling of a right cervical lymph node (level Ⅴ). Laboratory data were within normal limits, except for a slightly elevated serum total bilirubin level (1.4 mg/dl) and a positive result of hepatitis C virus antibody test. Fine needle aspiration cytology of the swelling showed a mucoepidermoid carcinoma. Computed tomography (CT) revealed a mass lesion in his right parotid gland with a diameter of 55 × 44 × 38 mm (Fig. 1). He underwent extended total parotidectomy and neck lymph node dissection with combined partial resection of the skin, muscles, and mastoid. The histopathological diagnosis was SDC with multiple lymph nodes metastasis, pT4aN2bM0, pStage IVA (the 8th Edition of Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours). The tumor invaded the

dermis, but other surrounding tissues were intact. Venous and lymphatic infiltration was observed. Upon examination, all the surgical margins were free from tumor. After surgery, he underwent radiotherapy (total dose: 60 Gy/30 fr) and chemotherapy with platinum-based combination regimen; however, the cancer relapsed and metastasized, leading to the death of the patient at 1 year and 7 months after the surgery.

Pathological findings

Gross examination revealed the tumor to have an irregular margin and was lobulated, whitish, solid, and not encapsulated by a fibrous tissue. Histologically, the tumor was located in the parotid gland tissue (Fig. 2a) and infiltrated into the dermis. Moreover, the tumor comprised two histologically different components and transition between them (Fig. 2a). The large part contained tumor cells with irregularly shaped large nucleus and swollen nucleoli and abundant eosinophilic cytoplasm. A diffuse proliferation with alveolar and trabecular pattern (Fig. 2b) along with some hyaline sclerosis was observed. Mitosis was frequently observed. Intravascular infiltration and perineural infiltration were also observed. Comedonecrosis was rarely seen. Based on the above histopathological findings, SDC was considered. At the periphery of the lesion, we found a focus of another component where atypical double-layered ducts composed of inner ductal cells and outer myoepithelial cells were compactly proliferated (Fig. 2c). The inner ductal cells were cuboidal with slightly eosinophilic cytoplasm, and the outer myoepithelial cells had a clear abundant cytoplasm with few mitosis. This tumor was recognized as an EMC. In the transitional area between the SDC and EMC, a less clear double-layered structure was observed. Inner ductal cells with a large nucleus and swollen nucleoli resembled tumor cells of SDC. Outer neoplastic myoepithelial cells were maintained but were unclear (Fig. 2d).

For the confirmation of the diagnosis, SDC and EMC component were further subjected to a panel of immunohistochemical markers (Table 1), where almost all tumor cells of SDC were positive for androgen receptor (AR) (Fig. 3a), HER2 (Fig. 3b). A small number of tumor cells were positive for gross cystic disease fluid protein-15 (GCDFP-15) in the SDC component. Conversely, in the EMC component, outer myoepithelial cells were positive for p63 (Fig. 3c) and WT1 and focally positive for p40, smooth muscle actin (SMA), S-100 (Fig. 3d), glial fibrillary acidic protein (GFAP), and DOG1, whereas inner ductal cells were positive for EMA (Fig. 3e). Cytokeratin AE1/AE3 was strongly positive in the inner ductal cells but was weakly positive in the outer myoepithelial cells. The Ki-67 labeling index was approximately 30% (hot spot) in the SDC component and 10% (hot spot) in the EMC component. In the transitional

area, enlarged inner ductal cells were focally positive for AR (Fig. 3f), and the outer myoepithelial cells were focally positive for p63 (Fig. 3g), p40, SMA, S-100, GFAP, DOG1, and WT1 (Fig. 3h).

Discussion

EMC is a rare biphasic tumor of the salivary gland and accounts for <5% of all salivary gland malignancies [1]. Local recurrence and lymph node metastasis are observed but EMC is generally considered as low-to-intermediate-grade carcinoma with relatively good prognosis, contrary to SDC. Histologically, EMC appears to be a double-layered duct composed of inner ductal cells and outer clear myoepithelial cells. In immunohistochemistry, neoplastic myoepithelial cells are positive for vimentin, SMA, p63, p40, GFAP, WT1, and S-100. In recent years, the expression of DOG1 in neoplastic myoepithelium has been demonstrated [7].
One of the most important differential diagnosis of EMC is PA. In the present case, the patient had a past history of PA of the parotid gland. We could not confirm the diagnosis of PA by reviewing histological sections, because they were not available. In the tumor concerned, a low-grade component of the tumor was diagnosed as EMC due to three evidences. Firstly, chondromyxoid stroma was not significant. Secondly, the myoepithelial cell layer was distinct from the stroma, and lastly, the outer myoepithelial cells were focally positive for SMA and S-100 in immunohistochemistry. Basal cell adenoma, basal cell adenocarcinoma, and adenoid cystic carcinoma were excluded because the tumor infiltrated to the surrounding tissue and atypical double-layered ducts, which included S-100-positive outer neoplastic myoepithelial cells with clear cytoplasm, exclusively occupied the lesion.

Seethala *et al*. recently reported a case of EMC with remarkable apocrine metaplasia [8, 9] with decapitation secretion, nuclear pleomorphism, prominent nucleolus, and positive AR immunohistochemistry. Because these features were similar to those of SDC, they stated a hypothesis that EMC with apocrine metaplasia could be a precursor lesion of the “hybrid tumor” of EMC and SDC.

A hybrid tumor is defined as a neoplasm composed of two or more disparate patterns that are not included in each other’s histological realm according to the literature [10]. Carcinoma ex PA is excluded from this category. Because our case included EMC and SDC component, we corroborate our case to be of a hybrid tumor. Furthermore, in the transitional area, atypical inner ductal cells of double-layered ducts showed remarkably large nucleus and were focally positive for AR and GCDFP-15 in

immunohistochemistry similar to SDC. p63-positive neoplastic myoepithelial cells in the outer layer were positive for WT1 and DOG1 that does not recognize normal myoepithelium. Therefore, SDC may have likely originated from the inner ductal cells of EMC but not developed *de novo* and consequently formed a "hybrid tumor". Thus, we validated the hypothesis put forth by Seethala *et al*. [8,9].

We searched PubMed using keywords "hybrid tumor" and "parotid gland" and found 19 cases of hybrid tumors of the parotid gland, in which both/all of the components were reported as malignant (Table 2) [2-6,11-16]. As far as we know, this is the third case of a hybrid tumor composed of SDC and EMC of the parotid gland. In Kainuma's case [6], the tumor was almost equally occupied by the SDC and EMC components. The tumor cells of the SDC component showed a cribriform growth pattern and comedonecrosis. In our case, the SDC component was significantly dominant (more than 90% of the tumor mass) with a minor component of EMC. The tumor cells of the SDC component were less differentiated with alveolar and trabecular pattern. This difference may be due to the different phases of the developmental sequence from typical EMC to hybrid tumor. In 20 cases including our case with hybrid tumor of the parotid gland, 10 cases were associated with EMC [3,5,6,12,13,16], 10 cases with SDC [2-6,15], 6 cases with adenoid cystic carcinoma [3,4,5,14,16], 4 cases with acinic cell carcinoma [2,4,5,11], 4 cases with basal cell adenocarcinoma [5,14,16], and a few cases with mucoepidermoid carcinoma [3,11,12], squamous cell carcinoma [5], myoepithelial carcinoma [5,15], polymorphous low-grade adenocarcinoma [4], and lymphoepithelial carcinoma [13]. It is interesting that EMC is frequently associated with hybrid tumor, although EMC is a relatively rare salivary neoplasm. The reason for the high frequency of EMC in hybrid tumors remains unclear, but it may be partly explained by a possibility that several other neoplasms, including PA, could have been incorrectly diagnosed as EMC.

Recently, the concept of "dedifferentiation" of the tumor, which has been widely accepted in bone and soft tissue pathology, is being extended to the salivary cancers. Dedifferentiation is defined as the progression of cells toward a less differentiated state in which the original line of differentiation is no longer evident [17]. Dedifferentiated carcinoma holds another aspect that it is basically composed of a primary low-grade carcinoma and high-grade malignant dedifferentiating components, such as adenocarcinoma, not otherwise specified, or large cell carcinoma, which is supposed to be derived from the low-grade component. These means that the phenomenon dedifferentiation holds two different aspects; high-grade carcinoma secondarily arising from pre-existing low-grade carcinoma and the status of differentiation in the pre-

existing tumor which has remarkably deviated from that in the derivative tumor. In general, the former aspect is more significant, and at this point, the term high-grade transformation could be more directly used. However, the separation of use between these two terms have not been clearly established. Our case meets not only the former aspect bur also the latter one, because pre-existing EMC produced a significantly high-grade component, that was equivalent to a histological type named as SDC but had remarkably deviated from original status of differentiation in EMC. Therefore, we could regard that diffusely invasive SDC arose from pre-existing EMC through dedifferentiation, and that, as a result of dedifferentiation, a hybrid tumor composed of EMC and SDC has appeared secondarily.

The nomenclature of a hybrid tumor and dedifferentiated carcinoma has often been confusing as reported previously. It is desirable for the elucidation of pathogenesis and epidemiology of hybrid tumor and dedifferentiated carcinoma to define distinctly these entities and to use the correct nomenclature. However, the description “hybrid tumors would not show evidence of evolution from one entity to another” in the diagnostic criteria of hybrid tumor was deleted in the second edition of Gnepp’s Diagnostic Surgical Pathology of Head and Neck [18]. If this revision is accepted, the difference between hybrid tumor and dedifferentiated carcinoma will be very unclear, and we would have to consider that a subset of hybrid tumors may result from dedifferentiation. Furthermore, there could be an overlapping realm of both the concepts that is histologically indistinguishable. Our case could be regarded as an example of the overlapping realm concept.

In conclusion, we presented a case of a hybrid tumor of EMC and SDC with the detailed histological observation and immunohistochemical study suggesting the origination of SDC from inner cells of EMC. Our case could be considered as a rare example of dedifferentiated carcinoma from EMC as well as a hybrid tumor.

References

1. Adel K *et al*. WHO Classification of Head and Neck Tumours. Lyon: IARC press.; 2017, pp. 173-175.
2. Seifert G *et al*. Hybrid tumors of salivary glands. Definition and classification of five rare cases. Eur J Cancer B Oral Oncol. 1996;32:251-9.
3. Croitoru CM *et al*. Hybrid carcinomas of the salivary glands. Report of 4 cases and review of the literature. Arch Pathol Lab Med. 1999;123: 698-702.
4. Zardawi IM. Hybrid carcinoma of the salivary gland. Histopathology. 2000;37:283-4.
5. Nagao T *et al*. Hybrid carcinomas of the salivary glands: report of nine cases with a clinicopathologic immunohistochemical, and p53 gene alteration analysis. Mod Pathol. 2002;15:724-33.
6. Kainuma K *et al*. Hybrid carcinoma of the parotid gland: report of a case (epithelial-myoepithelial carcinoma and salivary duct carcinoma) and review of the literature. Acta Otolaryngol. 2010;130:185-9.
7. Chênevert J *et al*. DOG1: a novel marker of salivary acinar and intercalated duct differentiation. Mod Pathol. 2012;25:919-29.
8. Seethala RR *et al*. New variants of epithelial-myoepithelial carcinoma: oncocytic-seba-ceous and apocrine. Arch Pathol Lab Med. 2009;133:950-9.
9. Seethala RR. Oncocytic and apocrine epithelial myoepithelial carcinoma: novel variants of a challenging tumor. Head Neck Pathol. 2013;7:S77-S84.
10. Gnepp DR *et al*. Salivary and lacrimal glands. In: Gnepp DR, editor. Diagnostic Surgical Pathology of the Head and Neck. Philadelphia: WB Saunders Co.; 2000, pp. 325-430.
11. Ballestin C *et al*. Combined acinic cell mucoepidermoid carcinoma of the parotid gland. Report of a case with immunohistochemical study. APMIS. 1996;104:99-102.
12. Chetty R *et al*. Hybrid carcinomas of the salivary glands. Arch Pathol Lab Med. 2000;124:494-6.
13. Piana S *et al*. Epstein-Barr-positive lymphoepithelial carcinoma and epi-myoepithelial cell carcinoma of the parotid gland: a hitherto unreported example of hybrid tumor. Virchows Arch. 2004;445:425-8.
14. Murphy JG *et al*. Salivary hybrid tumor: adenoid cystic carcinoma and basal cell adenocarcinoma. Virchows Arch. 2006;448:236-8.
15. Atay G *et al*. Hybrid carcinoma of the parotid gland: ductal carcinoma and myoepithelial carcinoma. Kulak Burun Bogaz Ihtis Derg. 2014;24:46-49.

16. Sabri A *et al*. Hybrid tumor of the parotid gland: a case report and review of the literature. Case Rep Otolaryngol. 2015;2015:192453.
17. Katoh M *et al*. An orderly retreat: dedifferentiation is a regulated process. Proc Natl Acad Sci U S A. 2004;101:7005-7010.
18. Gnepp DR *et al*. Salivary and lacrimal glands. In: Gnepp DR, editor. Diagnostic Surgical Pathology of the Head and Neck. 2nd ed. Philadelphia: Saunders.; 2009, pp. 413-562.

Figure legends

Fig. 1 CT scan demonstrates a mass lesion located in the right parotid gland (circled). Horizontal plane.

Fig. 2 Histological findings of the tumor.
a. The tumor is located in the parotid gland tissue and comprised of two histologically different components. Near two components, there is a transitional area. Hematoxylin eosin (HE) stain, original magnification ×20. Salivary duct carcinoma (SDC) component (left); Epithelial-myoepithelial carcinoma (EMC) component (upper right); Transitional area (lower right).

b. Histology of SDC. Large atypical tumor cells diffusely proliferate in solid pattern. Mitosis is frequent. HE stain, ×400.

c. Histology of EMC. Atypical double-layered ducts are composed of inner ductal cells and outer myoepithelial cells. HE stain, ×400.

d. In transitional area, double-layered structure is less clear than EMC. Inner ductal cells show a large nucleus with swollen nucleoli. HE stain, ×400.

Fig. 3 Results of immunohistochemistry.
In SDC component, almost all of tumor cells are positive for androgen receptor (AR) (a) and HER2 (b). In EMC component, outer myoepithelial cells are positive for p63 (c) and positive for S-100 (d). Inner ductal cells are positive for EMA (e). In transitional area, enlarged inner ductal cells are focally positive for AR (f). Outer myoepithelial cells are focally positive for p63 (g) and WT1 (h). Original magnification ×400.