Salivary Duct Carcinoma of the Parotid Gland: A Report of Two Cases and Literature Review

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Abstract
Salivary duct carcinoma (SDC) is one of the rarest and most aggressive forms of salivary gland malignancy, and is more likely to affect older male patients. A diagnosis of SDC for any patient has historically been associated with a poor prognosis, with a high incidence of both loco-regional and distant metastases. We report two cases of SDC of the parotid gland. They were treated by parotidectomy and ipsilateral neck dissection followed by postoperative irradiation. However both patients died of multiple lung metastases relatively early, showing that SDC is a highly aggressive form of parotid malignant tumor. Here, in the light of the literature, we discuss the value of focusing on over-expression/amplification of HER-2 and androgen receptors as well as the clinical usefulness of trastuzumab and anti-androgen therapy.

INTRODUCTION
Salivary duct carcinoma (SDC) is one of the most uncommon and aggressive forms of parotid tumor. It is more likely to affect older male patients, and has early regional and distant metastases. Two of 38 cases of malignant tumor of the major salivary gland at our institutions from 1986 to 2009 were pathologically diagnosed as SDC and are presented here together with discussion in consideration of the literature.

CASE PRESENTATION
Case 1
A 56-year-old man was referred for a painless swelling of the left parotid region, of three years' duration. A necrotic squamous cell carcinoma had been diagnosed by open biopsy by a surgeon at another hospital. The region was firm, 22mm in diameter and comprised swelling in five lymph nodes (Figure 1). The patient did not have facial paralysis. A round mass was detected on the left as a high-density area by CT, and a low-density area by MRI (Figure 2). A galliumscintigram showed uptake in both the parotid tumor and lymph nodes. Chest x-ray examination showed no evidence of metastasis. We made a pathological diagnosis of SDC of the parotid gland by open biopsy under local anesthesia. Histochemistry findings were keratin (+), EMA(+), S-100(-) and myosin(-). Parotidectomy with selective ipsilateral neck dissection was performed, followed by postoperative irradiation (50Gy). The left facial nerve was preserved (pT2N2b). The cut surface of the extirpated tumor specimen was milky-white in color (Figure 3). Histopathological examination of the tumor showed proliferation of tumor cells with eosinophilic cytoplasm and nuclear dense chromatin-associated central necrosis (Figure 4). After 15 months, multiple lung metastases were detected (Figure 5). Docetaxel was administered as follows: 100mg/day, 3-4 weeks, 4 cycles. After that, TS-1 (tegafur, gimeracil, oteracil, potassium) was administered continuously, but he died of cancer 4.5 years after the operation.

Case 2
A 72-year-old man was referred for a painful red swelling of the right parotid region of four months duration. The patient had past history of gastric cancer surgery. The swelling was firm, immobile and 34mm in diameter, without lymph node swelling. The patient
DISCUSSION

Salivary duct carcinoma (SDC) was first described by Kleinsasser et al. in 1968[2]. It is an aggressive adenocarcinoma, similar to a high-grade mammary duct carcinoma. SDC is one of the rarest and most aggressive forms of parotid tumor. The pathohistological entity of SDC was included in the second version of the WHO classification of salivary gland tumors in 1991[3]. Since then case reports have been increasing annually and have been associated with marked progression and a bad prognosis [4]. Incidence of the tumor was highest in the parotid gland followed by the submandibular gland, in older male patients. However, Jamal AM et al. reported a rare case in a young patient, a 22-year-old male, who survived for 10 years after an operation and postoperative irradiation [5]. It is often accompanied by facial paralysis and misdiagnosed as Bell’s paralysis [6].

A round mass on the right invading the facial skin was detected as a high-density area by CT. In fine needle aspiration cytology only malignancy was evident. A chest x-ray examination showed no evidence of metastasis. Total parotidectomy including part of the overlying skin and ipsilateral neck dissection (pT4apN1M0) were undertaken, followed by postoperative irradiation (56Gy). The right facial nerve adjacent to the tumor was sacrificed without reconstruction. SDC of the parotid gland was pathologically diagnosed and there was nerve invasion. Histochemistry showed that the tumor was positive for human epidermal growth factor receptor 2 (HER-2) and androgen receptor (AR), and negative for estrogen receptor and progesterone receptor [1]. One year after the operation lung metastasis was detected and lower lobectomy was performed. However, the patient died four years later due to disease progression.

Figure 1 Swelling of the left parotid region (case 1).

Figure 2 Computed tomography scan (A) and magnetic resonance imaging (B) showing a solid mass in the left parotid gland with no clear margin (arrow) (case 1).

Figure 3 Surgical specimen showing milky white cut surface (case 1).

Figure 4 Histopathologic findings for salivary duct carcinoma. H&E-staining, original magnification x50 (A) Carcinomatous elements with central comedo-like necrosis. (B) Epithelial polygonal tumor cell proliferation with eosinophilic cytoplasm (case 1).

Figure 5 CT showing multiple lung metastases (arrow) (case 1).
parotidectomy with neck dissection, with/without postoperative irradiation, has been proposed as the treatment modality.

The prognosis of this tumor is very dismal with: 26~66% (33%) local recurrence, 52.9~60.0% neck metastasis and 50~66% (46%) distant metastasis to lung, bone, liver etc. [6]. Five-year survival has been 11~30% and median survival 29 months in the recent literature. Our two cases were patients who were operated on, followed by postoperative irradiation, but both died of multiple lung metastases. In case 1, chemotherapy with docetaxel was administered for the lung metastasis but only slightly extended the patient’s life span. Few useful drugs have been proposed. Sato et al. reported an 83.3% 5-year overall survival rate for seven patients who underwent radical surgery following postoperative chemoradiation and adjuvant chemotherapy [7].

The biologic behavior of this tumor and its immunohistochemical characteristics has been analyzed. Jaehne et al. showed that SDC was characterized by a very high proliferation rate of Ki-67. Expression of HER-2/neu and p53 was statistically linked (p<0.05) to early local disease recurrence, distant metastasis, and survival rates in 50 cases of SDC [8]. These markers would likely reflect progression, associated with a highly malignant tumor entity like SDC. Immuno cytochemical investigation of SDC revealed constant over-expression of c-erbB2 as detected by membrane accentuation, and highly proliferative activity as detected by nuclear positivity for Ki-67 [9]. Lewis JE et al. reported that of 24 SDC cases studied by flow cytometry, DNA was diploid in five (21%), and non diploid in 19 (79%) and of the non diploid cases, 14 were aneuploid, 2 were multiploid, and 3 were tetraploid accounting for aggressive growth, high incidence of early lymph node metastasis, and frequent local recurrences after surgical excision. Metastases occur at distant sites, including the lungs, bone and liver.

Molecular targeted drug therapy using trastuzumab (Herceptin®) is now recommended for recurrent mammary cancer patients with over-expression/amplification of HER-2 protein. Trastuzumab is effective in increasing disease-free interval and prolonging overall survival for patients with ductal carcinoma of the breast [10]. Nabili et al. noted that immunohistochemical exploration for HER-2 protein may be contributive to SDC [11]. It has been reported that in patients with SDC, over-expression of HER-2 or androgen receptor (AR) are observed [12], and usefulness of trastuzumab has been observed in a recurrent SDC patient with over-expression of HER-2 [13]. In an evaluation of 15 cases of SDC for HER-2/neu over-expression using immunohistochemistry, Skalova et al. observed over-expression in all but one case of SDC, and suggested that anti-HER-2/neu therapy with trastuzumab was beneficial for patients with aggressive SDC [14]. Kuroda et al. reported successful treatment of a patient with advanced SDC using both anti-androgen therapy and chemotherapy using paclitaxel [15]. From the viewpoint of HER-2/neu over-expression and positive androgen receptors, suppression of tumor progression could have been expected by administering adjuvant drugs (such as trastuzumab, anti-androgenic agents) to case 1 patient.

In the case of parotid SDC, total parotidectomy and ipsilateral functional neck dissection seems justified, even for patients with T1 tumors. This is because local disease recurrence in such patients is often life-determining. If facial paralysis is present, a radical parotidectomy is mandatory. We believe that adjuvant measures, such as treatment with molecular targeted drugs and/or anti-androgen therapy, should be taken.

**CONCLUSION**

A diagnosis of SDC for any patient has historically been associated with a poor prognosis, with a high incidence of both loco-regional and distant metastases. We have presented two rare cases of SDC of the parotid gland. They were treated by parotidectomy with ipsilateral neck dissection followed by postoperative irradiation. However, both patients died of multiple lung metastases relatively early, indicating that SDC is one of the most aggressive forms of parotid tumor. In the light of the literature, we have discussed the value of focusing on over-expression/amplification of HER-2 and androgen receptors as well as the clinical usefulness of trastuzumab and anti-androgen therapy.

**REFERENCES**

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