Introduction

Salivary duct carcinoma (SDC) is an extremely rare and highly aggressive salivary gland malignancy with poor prognosis. Kleinsasser et al., were the first to report SDC in 1968 (1). SDC is estimated to account for 1-3% of all salivary gland malignancies (2,3,4). It has a poor prognosis due to its rapid growth, distant metastasis, early regional metastasis, and high rate of recurrence (2). The parotid gland is the most common site of involvement (2-5). SDC may also be observed in the submandibular and minor salivary glands, predominantly in the palate (2). Surgical resection of the tumor and ipsilateral neck dissection followed by chemotherapy and radiotherapy is currently the most common treatment protocol for SDC (4).

The local recurrence, lymph node metastasis and distant metastasis rates of SDC are 30%, 60%, and 30% to 70%, respectively (5). The lungs and the bones are the most common sites of distant metastasis; however, metastasis to the liver, skin and brain has also been reported with lower frequency (6).

Herein, we present a case of SDC of the parotid gland in a 62-year-old male patient with unusual skin and brain metastases 6 years after total parotidectomy and radical neck dissection of the primary tumor.

Case Report

A 56-year-old male patient was referred to the oral and maxillofacial surgery department for evaluation of a large painless swelling in his right parotid gland region. Facial asymmetry due to the lesion was noticeable. There was no pain, paresthesia or lymphadenopathy. No pus drainage was evident in extraoral and intraoral examination; the regional skin and the tissue mass were intact. The patient’s past medical history was unremarkable. The patient reported swelling since 3 months ago. The patient underwent computed tomography of the head and neck, which revealed an ill-defined lesion in the right parotid gland that was attached to the superficial skin (Figure 1).

An incisional biopsy was performed and histopathological examination revealed a malignant salivary gland tumor composed of islands and sheets of large epithelial cells with numerous ductal structures and comedo necrosis (Figure 2).
Salivary Duct Carcinoma with Late Distant Brain and Cutaneous Metastasis

Fig. 1. Radiographic view showing an ill-defined lesion in the right parotid gland, which is attached to the superficial skin.

Fig. 2. Microscopic features of the tumor. (a) Sheets of dysplastic cells with ductal structures. Note the comedo necrosis in the top right side (H & E staining, ×100). (b) Atypical mitotic features in tumoral cells (H & E staining, ×400)

Severe pleomorphism and atypical mitotic features were also seen. The most probable diagnosis was high-grade carcinoma most compatible with high-grade SDC. Immunohistochemical staining was performed to confirm the diagnosis. The tumoral cells showed positive staining for CK7 and androgen receptor (AR) (Figure 3).

Over 40% of tumoral cells showed positive staining for Ki67. The tumoral cells were negative for S100, estrogen receptor and progesterone receptor. These findings were in favor of high-grade SDC of the parotid gland. Thus, total parotidectomy was carried out followed by adjacent radiotherapy (Figure 4).

The patient had no noticeable complication at the 6-year follow-up; however, in his next follow-up session, an exophytic ulcerated small lesion was detected at the previous surgical site. The entire lesion was surgically excised with 2 mm of safe margin (Figure 5). Microscopic examination of the lesion revealed the same features as the previous lesion with free surgical margins. Considering the history of total parotidectomy and development of a new skin lesion at the same site 6 years later, we presumed that the new lesion more probably was a delayed metastatic skin lesion. Although the lesion could be a late local recurrence possibly due to implantation or seeding of the tumoral cells during the previous surgical procedure, but local recurrence was expected to happen earlier than 6 years. The patient underwent full body examination to find any other possible distant metastatic lesion. Computed tomography of the head and neck revealed one ill-defined lesion in the brain (Figure 5). Unfortunately, the patient died 2 weeks after surgical resection of the brain lesion.
Fig. 4. Surgical excision of the lesion. a) Pre- and retro-auricular incision for total parotidectomy. (b) Complete excision of tumor

Fig. 5. Distant metastasis of the tumor. (a) Excised skin lesion with 2 mm of safe margin (b) Brain metastasis

Discussion

SDC of the parotid gland is a malignant tumor with an aggressive clinical course and occasional lung metastasis. Detection of SDC cells in the skin tissue several years after total tumorectomy is an extremely rare occurrence. SDC has a tendency to invade the
surrounding tissue and has a high metastatic potential via the hematogenous and lymphatic pathways (4,7). SDC shows an aggressive clinical course with poor prognosis, and over 70% of patients die within 3 years after the primary diagnosis (7). Although our patient survived for more than 6 years after the primary diagnosis, he died due to late distant metastasis.

SDC is usually a high-grade malignant tumor, but low-grade SDC and intraductal SDC have also been reported (8). High-grade SDC is histopathologically characterized by proliferation of dysplastic cells containing large round to oval nuclei with conspicuous nucleoli and rich eosinophilic cytoplasm, occasionally accompanied by comedo necrosis, which resembles high-grade breast carcinoma. The immunohistochemical characteristics of SDC cells include positive staining for human epidermal growth factor receptor (HER) 2, AR and CK7 (2,4). Since most salivary gland malignancies have positive immunoreactivity for CK7, immunoreexpression of this protein may provide valuable information to differentiate primary salivary gland carcinomas from metastatic tumors (9). SDC usually shows negative results for expression of S-100, p63 and smooth muscle myosin (8). Our patient showed positive immunostaining for CK7 and AR.

SDC shows a high frequency of lymph node metastasis and distant metastasis to the lungs, liver, brain, and bones. In this study, we presented a case of SDC of the parotid gland in a 62 year-old man with unusual metastases to the skin and brain 6 years after primary treatment. Based on this fact that metastasis of SDC to the skin tissue is very uncommon and the cutaneous lesion happened in the primary site of the lesion, late local recurrence could be considered. On the other hand, local recurrence was expected to happen sooner than 6 years. It seemed that an unusual cutaneous metastasis was the most probable diagnosis. The above-mentioned points indicate the aggressiveness and poor prognosis of SDC.

Although complete surgical resection and ipsilateral neck dissection followed by postoperative radiation comprise the standard treatment for SDC (10-12), the reported survival rate is 43% for the 5-year disease-specific survival and 36% for the disease-free survival (2,13). Johnston et al. reported that 37.5% of the patients with local and regional recurrence of SDC showed distant metastases (14). The majority of them received palliative therapy and supportive care, although some of them underwent salvage surgery with additional radiation therapy (14).

In this case, we highlighted the importance of having a high insight in evaluation of highly aggressive tumors such as SDC for atypical findings during periodic follow-ups especially in long-term. It seems that routine surgical treatment may not be enough even in cases with no distant metastasis at the time of initial diagnosis. Considering the aggressive nature of SDC, chemotherapy accompanied by surgical treatment may be the best approach for patients with SDC. Although systemic chemotherapy should be considered to minimize the risk of distant metastasis of SDC, there is no convincing evidence supporting the optimal efficacy of chemotherapy for SDC. On the other hand, a previous study claimed that chemotherapy was not effective for SDC, and SDC cells were resistant to chemotherapy (14). Recently, Kawahara et al. reported that although cetuximab monotheraphy was not sufficient to control tumor growth in SDC, cisplatin/5-FU chemotherapy plus cetuximab was effective for treatment of lung metastasis of SDC (3).

Some prognostic factors have been suggested for SDC prognosis. In major salivary glands, tumor size > 3 cm, patient’s age over 50 years, lymph node involvement, high tumor grade, perineural invasion, positive surgical margins, and regional and distant metastases may indicate poor prognosis (2,15,16). In addition, overexpression of HER2/neu and p53 has been reported as a poor prognostic factor for early regional recurrence, distant metastasis, and eventually lower survival rate (17). Considering the overexpression of HER2/neu in SDC, anti-HER2 monoclonal antibodies (trastuzumab) have been suggested for targeted therapy of advanced SDC HER2/neu-positive tumors (18). Williams et al. found that both AR and estrogen receptor β-negative SDC were significantly correlated with a lower survival rate (17). This finding may explain the poor prognosis of our reported AR-positive case with delay distant metastasis. For AR-positive SDCs, androgen deprivation therapy has also been evaluated as a treatment option (19,20). Along with these studies, we suggest that AR positivity in SDC may be correlated with poor prognosis and can be used for targeted therapy of AR-positive SDCs. Further studies are required to assess the effectiveness of targeted therapy for advanced SDCs.

**Conclusion**

We reported a 62-year-old male patient with SDC of the parotid gland with unusual metastases to the skin of the primary site and brain 6 years after the primary treatment. Despite the comprehensive treatment composed of total parotidectomy and radiotherapy, the patient died 6 years after surgery because of late distant metastasis to the brain. These findings highlight the aggressiveness, poor prognosis and low rate of disease-specific and disease-free survival of SDC and also the need for long term follow up and further knowledge about the available treatment options for management of this tumor.

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**Conflict of Interest**

The authors declared that there is no conflict of interest regarding the publication of this article.
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