Case Report

Journal of Dental and Maxillofacial Surgery

Salivary Duct Carcinoma with Neuroendocrine Differentiation: Report of a Confusing Case Arising in the Parotid Gland

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Received date: Jan 10, 2021; Accepted date: Feb 11, 2021; Published date: Feb 18, 2021

Abstract

We here report an extremely rare case of salivary duct carcinoma with neuroendocrine differentiation. The patient was a 60-year-old Japanese male who presented with facial palsy that had persisted for two months and was referred to a local university hospital. Open biopsy resulted in a diagnosis of parotid carcinoma and radical parotidectomy and cervical dissection were performed. Histopathological examination revealed a tumor consisting of irregular, large and small invasive nests with numerous luminal structures that, in the larger solid nests, were often accompanied by comedo necrosis. Intraductal growth was seen surrounding the tumor. Immunohistochemically, the tumor cells were positive for androgen receptor along with AE1/AE3, CAM5.2, 34betaE12, and CK7. There were also reactions for synaptophysin and CD56, but not for chromogranin A. The histopathological features of, and diagnostic problems related to, neuroendocrine carcinoma are discussed.

Keywords: Salivary duct carcinoma, High-grade carcinoma, Neuroendocrine differentiation, Parotid gland, Large cell neuroendocrine carcinoma

Introduction

Salivary duct carcinoma (SDC) is histologically similar to ductal carcinoma of the breast and is now recognized as high-grade carcinoma of the salivary glands [1,2]. It usually occurs in the parotid gland of elder male, but also in the intraoral minor salivary glands, and is known to have various special subtypes [3-5]. Although heterogeneity in immunohistochemistry of SDC is already known, its neuroendocrine differentiation is quite exceptional. This unusual feature has not been clearly stated in nowadays representative textbooks including the current 4th edition of World Health Organization (WHO) classification of Head and Neck Tumors.

Herein, we describe a case of SDC that occurred in the parotid gland and showed unusual neuroendocrine differentiation.

Case Report

The patient was a 60-year-old Japanese male who presented with facial palsy that had persisted for 2 months and was referred to a local university hospital. No particular past medical history, family history or social history was noted.

An open biopsy resulted in a diagnosis of “parotid carcinoma” and radical parotidectomy and cervical dissection were performed. Post-operative radiotherapy...
was carried out with X-ray dose of 60Gy/30fr, combined with chemotherapy involving cisplatin of 100mg/m² in each course for two times. There have been no signs of recurrence or metastasis for approximately two years after surgery.

Pathological findings

Macroscopically, the lesion was an approximately 3 cm diameter milky white lobulated mass with an irregular margin and was surrounded by enlarged lymph nodes (Figure 1).

![Figure 1](image1.png)

**Figure 1:** Gross operative specimen after radical parotidectomy.

Histopathological examination revealed a tumor consisting of irregular, large and small invasive nests with numerous luminal structures that, in the larger solid nests, were often accompanied by comedo necrosis (Figures 2, 3a and b). Around the tumor, the serous acini were atrophied and destroyed. Nearby, intraductal growth was observed with flat myoepithelial cells or small round basal cells surrounding relatively well-demarcated tumor nests (Figure 3c and d). Perineural invasion was remarkable also in the histological sections. Lymph node metastases were identified in regional and cervical lymph nodes.

Finally, the tumor was classified as pT4aN2bM0, pStage IVA in accordance with the 8th Edition of Union for International Cancer Control (UICC) TNM classification of malignant tumors.

Immunohistochemically, the tumor cells were negative for GCDFP15, but positive for androgen receptor (AR) along with various cytokeratins (CKs) such as AE1/AE3, CAM5.2, 34betaE12, and CK7 (Figure 4a-c). CK20 was negative. In part of the intraductal growth, flattened or small cells positive for CK5/6 (Figure 4d), p63 and p40 were seen surrounding the tumor nests (Figure 5a and b); these cells were considered to correspond to the myoepithelial and basal cells mentioned above. There were also reactions for synaptophysin and CD56 (Figure 5c and d); however, the cells were negative for chromogranin A and Grimelius stain.

![Figure 2](image2.png)

**Figure 2:** Light microscopy image shows the tumor forming irregular, large and small nests.

Discussion

SDC is listed as a highly malignant carcinoma with a poor prognosis. It used to be highlighted by Delgado et al. [1] and Barnes et al. [2] in the 1990s, and is currently recognized as one of the best known histological types of salivary gland tumors.

As the name implies, it is histologically similar to ductal carcinoma of the breast, with which it some histological features in common. However, the immunohistochemical characteristics differ considerably: ER and PgR, which are positive in most breast cancers, being negative in SDC, and AR generally being positive.

In the present case, the tumor was considered to be poorly differentiated because some of the usual characteristics, such as Roman-bridging and cribriform pattern, were scanty with comedo necrosis being recognized, and because GCDFP15, which is an apocrine marker, was completely negative. In contrast, intraductal growth, which is a common feature of ductal carcinoma of the breast, was recognized relatively widely by light microscopy and immunohistochemistry.
Figure 3: Photomicrographs showing larger nests associated with prominent necrosis (a) and remarkable pleomorphism (b). In regions of intraductal growth, flattened myoepithelial cells or small round basal cells can be seen surrounding the structures (arrows) (c,d).

Another characteristic is color development with neuroendocrine markers. Various markers are currently used in diagnosis of so-called neuroendocrine tumors, chromogranin A and synaptophysin being typical examples. But, in the present case, the tumor cells were positive for synaptophysin and negative for chromogranin A. Because CD56 is by no means a highly specific marker, whether synaptophysin expression alone is a reliable marker is controversial. However, given that there is a fundamental difference in what these markers recognize, it has been shown that the same neuroendocrine cells can be chromogranin-positive and synaptophysin-negative, otherwise conversely synaptophysin-positive and chromogranin-negative as well [6].

Of note, it is known that incidental neuroendocrine differentiation can occur in ductal carcinoma of the breast [7,8]; similarly, there is one reported case of SDC having the potential for neuroendocrine differentiation [9].

Interestingly, van Krimpen et al. has detected coexpression of both chromogranin A and synaptophysin only in 9 out of 40 cases (23%) of breast carcinomas with neuroendocrine differentiation [10]. Most lesions of breast carcinomas with neuroendocrine differentiation are classifiable in the conventional categories of mammary carcinomas and no special prognostic significance is attached to these tumors [7,10].

Figure 4: Immunohistochemistry. The tumor is diffusely positive for AE1/AE3 (a) and AR (b,c). In regions of intraductal growth, positivity for CK5/6 is seen in the flat myoepithelial cells or small round basal cells surrounding the structures (d). Asterisk designates invasive foci without rimming of abluminal cells.
In recent years, large cell neuroendocrine carcinoma (LCNEC), which is similar to those of other organs such as the lung, has also been recognized in the major salivary glands [11,12]. Its histological characteristics are common to those of such tumors in other organs and include expression of neuroendocrine markers and “neuroendocrine morphology”, which is reflected in rosette formation, peripheral palisading, organoid structures, and a regular geometric ribbon-like arrangement. However, these characteristics were not apparent in the present case. Even if positivity for neuroendocrine markers had been identified, this would not have constituted definitive evidence of LCNEC, and it is necessary to pay sufficient attention to the presence or absence of neuroendocrine morphology. Thus, making a quick and easy diagnosis of LCNEC should be strongly discouraged.

![Figure 5: p63 (a) and p40 (b) showing similar locations to CK5/6. Asterisk designates invasive foci as well. The tumor cells are also positive for synaptophysin (c) and CD56 (d).](image)

Figure 5: p63 (a) and p40 (b) showing similar locations to CK5/6. Asterisk designates invasive foci as well. The tumor cells are also positive for synaptophysin (c) and CD56 (d).

It has long been known that, in addition to LCNEC, small cell carcinomas also occur rarely in the major salivary glands [13,14]. Conversely, low-grade tumors such as carcinoid tumors virtually do not exist in the salivary glands; thus, if a carcinoid tumor is diagnosed, the possibility of metastasis from the lungs or gastrointestinal tract should be seriously considered.

**Conclusion**

In the present case, we focused on positivity for so-called neuroendocrine markers on immunohistochemistry, and finally determined that the lesion was an SDC with the potential for neuroendocrine differentiation. However, regardless of the presence of neuroendocrine differentiation, diagnosis as a SDC is necessary and sufficient enough for such tumors, because no special prognostic significance is likely expected between SDCs with neuroendocrine differentiation and those without, just as in breast cancers. In that occasion, positivity for AR on immunohistochemistry as well as the characteristic intraductal growth that reflected its histogenesis should be focused. In addition, SDC is a high-grade carcinoma by nature and requires special clinical attention.

**Declarations**

**Ethics approval and consent to participate**
Not required.
All authors agreed to participate.

**Consent for publication**

The patient has agreed with publication of the article, and written consent has been retained in Hirosaki University Hospital.

No case details or other personal information and no images of the patient are used.

**Competing interests**

The authors have no conflicts of interest to declare.

**Funding:** None.

**Author contributions**

- Hiroshi Harada: Conceptualization, Writing - original draft, Writing - review & editing.
- Reiko Kudo: Visualization, Writing - review & editing.
- Atsushi Matsubara: Resources, Validation, Writing - review & editing.
- Akira Kurose: Supervision, Project administration.
References


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