**Case Report**

**Aggressive invasive micropapillary salivary duct carcinoma of the parotid gland**

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The presence of invasive micropapillary component has been reported to be associated with salivary duct carcinoma and poor outcomes. Herein is described a rare case of invasive micropapillary salivary duct carcinoma of the parotid gland in a 60-year-old man. The micropapillary component was approximately 70% of the area of the tumor. Squamous differentiation was focally seen adjacent to the micropapillary component. On immunohistochemistry the ordinary salivary duct carcinoma component was positive for gross cystic disease fluid protein-15 (GCDFP-15), androgen receptor (AR), and HER2/neu, whereas both micropapillary and squamous components were negative for GCDFP-15 and AR. Immunohistochemical staining for D2-40 highlighted the lymph vessel invasion of tumor cells. This patient developed metastases in the lymph nodes of the neck, and also in the liver, lung, and brain. The lymph nodes and liver metastases had both ordinary salivary duct carcinoma and micropapillary components. The patient died of tumor 11 months after the initial surgical operation. The results support that the presence of micropapillary component is associated with more aggressive behavior of salivary duct carcinoma. It is also important for pathologists to recognize that GCDFP-15 and AR expression can be reduced in micropapillary carcinoma in the differential diagnosis of metastatic tumor.

**Key words:** immunohistochemistry, micropapillary, parotid gland, salivary duct carcinoma, squamous

Salivary duct carcinoma is an aggressive adenocarcinoma that morphologically resembles high-grade ductal carcinoma of the breast.¹ A cribriform pattern with comedo necrosis is typically seen in salivary duct carcinoma. There are some histological variants of salivary duct carcinoma: sarcomatoid, mucin-rich, and invasive micropapillary variants.¹ Nagao et al. reported 14 cases of invasive micropapillary salivary duct carcinoma that occurred in the parotid gland and that were associated with a more aggressive clinical course than ordinary salivary duct carcinoma.² After that report there has been no additional report of invasive micropapillary salivary duct carcinoma in the English-language literature. Here we describe an additional case of invasive micropapillary salivary duct carcinoma of the parotid.

**CLINICAL SUMMARY**

A 60-year-old Japanese man was admitted to hospital due to swelling of the left parotid region. There was no sign of facial nerve palsy. Radiological examination indicated a tumor in the left parotid gland, accompanied by swollen lymph nodes of the neck. Surgical resection of the parotid tumor together with lymph node dissection was performed. Local recurrence and liver metastasis of tumor occurred at 6 months after the initial operation. Chemotherapy with 5-fluorouracil and cisplatin had no effect on the recurrent tumor. Lung and brain metastases developed, and the patient died due to the tumor at 11 months after the initial operation. Autopsy was not performed.

**MATERIALS AND METHODS**

The excised specimen was fixed in a solution of 10% formaldehyde and embedded in paraffin. Four micrometer-thick sections were prepared and stained with HE. Immunohistochemical staining was performed with the primary antibodies as follows: low-molecular-weight cytokeratin (CAM5.2, Becton Dickinson, San Jose, CA, USA; dilution 1:20), pancytokeratin (AE1/AE3, Neomarkers, Fremont, CA, USA; dilution 1:40), cytokeratin (CK) 7 (OVT-T12/30, Dako,
Glostrup, Denmark; dilution ×50), CK14 (LL002, Novocastra, Newcastle upon Tyne, UK; dilution ×50), CK20 (Ks20.8, Dako, Glostrup, Denmark; dilution ×50), high-molecular-weight cytokeratin (34bE12, Enzo Life Sciences, Farmingdale, NY, USA; dilution ×50), epithelial membrane antigen (EMA; E29, Dako, Carpinteria, CA, USA; dilution ×400), gross cystic disease fluid protein-15 (GCDFP-15; 23A3, Novocastra; dilution ×20), androgen receptor (AR; AR27, Zymed Laboratories, South San Francisco, CA, USA; dilution ×20), estrogen receptor (1D5, Dako, Carpinteria, CA, USA; dilution ×2), progesterone receptor (PgR36, Dako, Carpinteria, CA, USA; dilution ×6), and HER2/neu (rabbit polyclonal, Nichirei, Tokyo, Japan; dilution ×200). The subsequent development of antibody-bridge labeling using the Envision plus system (Dako, Carpinteria, CA, USA) with hematoxylin counterstaining was performed.

RESULTS

Macroscopically, the tumor was solid, whitish-gray, and focally yellow on cut surface, and was 2.3 cm in maximum diameter (Fig. 1). Intraparotid lymph node metastases were also present around the tumor. Histologically the tumor was composed of typical salivary duct carcinoma and invasive micropapillary component; the latter consisted of approximately 70% of the tumor area (Fig. 2a,b). The conventional salivary duct carcinoma area was composed of infiltrating growth of carcinoma cells arranged in nest or cribriform pattern with comedo necrosis. These carcinoma cells had abundant, eosinophilic cytoplasm, large pleomorphic nuclei and pleomorphic nucleoli. Focal dense sclerotic stroma was seen within the conventional salivary duct carcinoma, but there was no definite evidence of pre-existing pleomorphic adenoma. Invasive micropapillary carcinoma was characterized by morula-like cell clusters without fibrovascular cores surrounded by clear spaces (Fig. 2c). Squamous differentiation was focally seen adjacent to the micropapillary component (Fig. 2d). Immunohistochemistry results are given in Table 1. The EMA-positive reaction was stronger in peripheral cell membranes having an 'inside-out' staining pattern in
the micropapillary component (Fig. 3). Ordinary salivary duct carcinoma was positive for GCDFP-15 and AR, whereas both micropapillary and squamous components were negative for these markers (Fig. 4). Both ordinary salivary duct carcinoma and micropapillary components were positive for CK7 and HER2/neu, but negative for CK20. Immunohistochemical staining for D2-40 highlighted the lymph vessel invasion of tumor cells in part. But most of the clear spaces of the invasive micropapillary component were negative for D2-40. Myoepithelial or basal cells positive for CK14 focally surrounded conventional salivary duct carcinoma cells in a cribiform pattern, indicating intraductal spread.

**DISCUSSION**

Invasive micropapillary carcinoma component has been reported in the ovary, breast, colon, lung, and urinary bladder.
The biological behavior of salivary duct carcinoma.2 Likewise, 70% of the area, but there is no definite association between present case this component was found to be approximately

Table 1 Immunohistochemistry and histological components

<table>
<thead>
<tr>
<th>Marker</th>
<th>SDC</th>
<th>Micropapillary</th>
<th>Squamous</th>
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<tbody>
<tr>
<td>Cytokeratin (CAM5.2)</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Cytokeratin (AE1/AE3)</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Cytokeratin 7</td>
<td>+</td>
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<tr>
<td>Cytokeratin 20</td>
<td>–</td>
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<tr>
<td>HMW-CK (34bE12)</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>+</td>
<td></td>
<td>Weak+</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Estrogen receptor</td>
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<tr>
<td>Progesterone receptor</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>HER2/neu</td>
<td>–</td>
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carcinomas.3–9 Invasive micropapillary carcinomas have characteristic morphological features as shown by morula-like cell clusters without fibrovascular cores, surrounded by clear spaces. EMA is positive in peripheral cell membranes (so-called ‘inside-out’ staining pattern). Clinically, the presence of invasive micropapillary component is associated with more aggressive behavior in these carcinomas. It has been reported that invasive micropapillary carcinoma of the breast is associated with frequent lymph vessel invasion and lymph node metastasis.5 In salivary gland cancer this component can be seen in salivary duct carcinoma. Nagao et al. have reported 14 cases of invasive micropapillary variant of salivary duct carcinoma, most of which occurred together with lymph node metastasis (14/14), distant metastasis (9/14), and patient death (9/14).2 The present patient died of metastatic carcinoma 11 months after the initial surgery followed by radiation therapy and chemotherapy. This finding indicates that invasive micropapillary salivary duct carcinoma is an aggressive tumor.

The amount of invasive micropapillary component in salivary duct carcinoma ranges from 10% to >90%.2 In the present case this component was found to be approximately 70% of the area, but there is no definite association between the proportion of the invasive micropapillary component and the biological behavior of salivary duct carcinoma.2 Likewise, such association has not been observed in invasive micropapillary carcinoma of the breast.5 In the current case focal squamous differentiation was present adjacent to the micropapillary component. To the best of our knowledge, this is the first report regarding the presence of squamous component in invasive micropapillary salivary duct carcinoma.

Salivary duct carcinoma frequently expresses GCDFP-15 and AR.15 Nagao et al. have reported that invasive micropapillary salivary duct carcinomas express GCDFP-15 and AR in 10/12 (83%) and 9/12 (75%) cases, respectively.2 Interestingly, in the present case ordinary salivary duct carcinoma was positive for GCDFP-15 and AR, but the invasive micropapillary component and squamous component were negative for both markers. This finding suggests that morphological change may be associated with phenotypic change in salivary duct carcinoma. In addition, negative staining for GCDFP-15 and AR in the metastatic foci of invasive micropapillary carcinoma can lead to difficulty in determination of the primary site because various organs of carcinoma have an invasive micropapillary pattern, as mentioned here.

HER2/neu is a receptor tyrosine kinase, and its overexpression and/or gene amplification have been reported in various carcinomas, including breast and salivary gland.11,12 Most salivary duct carcinomas express HER2/neu, and some of them are associated with HER2/neu gene amplification.13,14 Nagao et al. have reported frequent expression of HER2/neu in invasive micropapillary salivary duct carcinoma, which is consistent with the present results.2 It has been reported that HER2/neu overexpression is associated with a poor prognosis in salivary duct carcinoma.15 Thus, overexpression of HER2/neu in the micropapillary component may contribute to highly aggressive behavior of this variant. Furthermore, this highly malignant tumor might respond to therapy with monoclonal antibody (Herceptin) directed against the extracellular domain of the HER2/neu protein. Further study is necessary to elucidate the clinical response to Herceptin therapy and its association with the levels of HER2/neu protein expression and gene amplification.

REFERENCES


