Case Report

The Importance of Postoperative Radiotherapy against Polymorphous Low-Grade Adenocarcinoma of the Parotid Gland: Case Report and Review of the Literature

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UEMAETOMARI, I., TABUCHI, K., TOBITA, T., TSUJI, S., WADA, T., KAMMA, H. and HARA, A. The Importance of Postoperative Radiotherapy against Polymorphous Low-Grade Adenocarcinoma of the Parotid Gland: Case Report and Review of the Literature. Tohoku J. Exp. Med. 2007, 211 (3), 297-302 —— Polymorphous low-grade adenocarcinoma (PLGA) of the salivary gland is a disease entity that is a recently described form of adenocarcinoma. PLGA most commonly arises in the minor salivary glands. We report two cases of PLGA of the parotid gland. Case 1: A 52-year-old female visited the University of Tsukuba Hospital with a painless mass in the left parotid region. A superficial parotidectomy and postoperative radiotherapy were performed. The patient has been free from disease for 50 months. Case 2: A 55-year-old female initially noticed a painless slowly growing mass in the left parotid region. The tumor was removed with a superficial parotidectomy. The local recurrence was found 6 years after the initial surgery. The recurrent tumor was removed, and radiotherapy was administered thereafter. The patient has been free from the disease for 33 months since the last treatment. The treatment for the primary lesion is crucial for the prognosis since metastasis to the regional lymph node or to distant region is unusual in PLGA. Although surgical extirpation is the recommended modality for treatment of PLGA, wide resection with a safety margin is often difficult in the parotid gland because of the presence of the facial nerve. Our two cases were successfully treated with surgery and postoperative radiotherapy. Although our literature search revealed 32 previously reported cases of PLGA of the parotid gland, only five of the 32 cases were treated postoperative radiotherapy. We highlight the importance of postoperative radiotherapy for PLGA of the parotid gland.

polymorphous low-grade adenocarcinoma (PLGA); parotid gland; major salivary gland

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Polymorphous low-grade adenocarcinoma (PLGA) is described as a malignant epithelial tumor characterized by cytological uniformity, morphological diversity and a low metastatic potential (Seifert and Sobin 1991). PLGA is the second most common intraoral malignant neoplasm arising in the minor salivary glands. However, to our knowledge, there have been only 34 reported cases of PLGA arising in the parotid gland (George et al. 1991; Mark et al. 1991, 1992; Miliauskas 1991; Ritland et al. 1993; Kemp et al. 1995; Merchant et al. 1996; Puxeddu et al. 1998; Gibbons et al. 1999; Nagao et al. 2004; Tamiolakis et al. 2004). PLGA has a low potential for distant metastasis and its prognosis is thought to be favorable.

To date, only a few attempts have so far been made to clarify the nature of PLGA arising in the parotid gland. This paper reports two cases of PLGA arising in the parotid gland, and the previous articles are reviewed.

CASE REPORT

Case 1

A 52-year-old female visited the University of Tsukuba Hospital with a painless mass in the left parotid region in February 2001. Computed tomography (CT) examination showed a slightly enhanced mass, 30 mm in diameter, in the superficial lobe of the left parotid gland (Fig. 1). The tumor was removed with a superficial parotidectomy in April 2001.

The resected tumor was well-circumscribed, measured 20 × 15 × 15 mm in size and the epithelial tumor cells showed various growth patterns (Fig. 2). These cells expanded the surrounding fat tissue, fibrous tissue and salivary gland. The

Fig. 1. An axial contrast CT scan before treatment (case 1).
An axial contrast CT scan of the parotid gland showed a tumor with a maximal diameter of 30 mm. Tumor enhancement was not uniform.

Fig. 2. Histological findings (case 1).
The tumor showed solid patterns (arrows) (A) and parallel cords (arrows) (B) of epithelial tumor cells. The tumor cells were cuboidal and had an oval and hyperchromatic nucleus with a prominent nucleolus. HE, bar = 100 μm.
tumor histologically showed various growth patterns (parallel cords and solid pattern) of epithelial tumor cells. The tumor cells were cuboidal and had an oval and hyperchromatic nucleus with a prominent nucleolus. Immunohistochemically, the tumor cells were positive for S-100 protein, cytokeratin (AE1/AE3), epithelial membrane antigen (EMA), keratin (CK5, 6, 8, 17, 19), and glial fibrillary acidic protein (GFAP), weakly positive for vimentin and negative for \( \alpha \)-smooth muscle actin (\( \alpha \)-SMA). Positivity for MIB-1 (Ki-67) was scant.

Postoperative radiotherapy was performed with a total dose of 60 Gy. The patient has shown no signs of recurrence for 50 months postoperatively.

**Case 2**

A 55-year-old female initially noticed a painless mass in the left parotid in 1987. She visited our hospital in April 1996 with a slow growing mass over this period. Facial nerve palsy was not observed. CT and magnetic resonance imaging (MRI) demonstrated a well enhanced tumor, 30 mm in diameter, in the superficial lobe of the left parotid gland (Fig. 3). The tumor was removed with a superficial parotidectomy.

The encapsulated oval tumor, 35 mm in diameter, was accompanied by a daughter nodule. Local metastasis was found around the subcutaneous region, the para-parotid connective tissue, and the lymph nodes (Fig. 4). The tumor consisted of homogeneous cuboidal cells with mild nuclear atypia and scant mitotic activity. The tumor cells occasionally formed small tubules in solid nets and marginally arranged in a glandular nest with

Fig. 3. An axial contrast MRI before treatment (case 2).

An axial contrast MRI of the parotid gland showed a tumor with a maximal diameter of 30 mm. The enhancing effect was strong.

Fig. 4. Histological findings (case 2).

The tumor consisted of homogeneous cuboidal cells with mild nuclear atypia and scant mitotic activity (arrows) (A). The tumor cells occasionally formed small tubules in solid nets and marginally arranged in a glandular nest with duct-like structures (B). HE, bar = 100 \( \mu m \).
duct-like structures. Tumor cells showed the same immunohistochemical reactivity as in case 1.

After the initial treatment, the patient was followed in our outpatient clinic. She presented with a painless mass in the left parotid region in April 2002. The tumor was thought to be a local recurrence. It was removed with an adequate safety margin and a course of irradiation was performed with a total dose of 60 Gy thereafter. The patient has not shown any signs of recurrence or metastasis for 33 months postoperatively.

**DISCUSSION**

**Clinical features of the PLGA of the parotid gland**

PLGA is a rare malignant neoplasm in the parotid gland. Therefore, it is useful to look more closely at some of the specific features of PLGA arising in the parotid gland. There have been 36 reported cases of PLGA arising in the parotid gland (Table 1) (George et al. 1991; Mark et al. 1991, 1992; Miliauskas 1991; Rilfand et al. 1993; Kemp et al. 1995; Merchant et al. 1996; Puxeddu et al. 1998; Gibbons et al. 1999; Nagao et al. 2004; Tamiolakis et al. 2004). The genesis was acceptable as de novo PLGA in eight cases and as ex pleomorphic adenoma in four cases. The reports of PLGA of the parotid gland were reviewed and clinicopathological features of 36 cases of PLGA of the parotid gland were compared to those of the minor salivary glands (total 204 cases) (Castle et al. 1999; Evans et al. 2000). The local recurrence, regional lymph node metastasis and distant metastasis rates of PLGAs arising in the parotid gland were 8/33 (24%), 1/33 (3.0%) and 0/33 (0%); while those arising in the minor salivary glands were 10.5-32.5%, 10% and 0.6-7.5%, respectively (Castle et al. 1999; Evans and Luna 2000). There was no apparent difference between the clinical features, male/female ratio or age distribution between PLGA of parotid gland and that of minor salivary glands.

**Pathological findings of PLGA of the parotid gland**

There have been several reports of pathological features and prognoses in PLGA arising in minor salivary glands. PLGA showing more than focal papillary growth clearly correlates with cervical lymph node metastasis (Evans and Luna 2000). However, the correlation between these findings and prognosis was not obvious in PLGA arising in the parotid gland.

In general, the mitotic figure and MIB-1 index represent cell proliferative activity. On pathological examination, scant or no mitotic figures have been reported in PLGA of the parotid gland. Furthermore, low reactivity to MIB-1 was demonstrated in our two cases, though a relation between cell proliferative activity and prognosis were not obvious. The differential diagnosis includes papillary cystadenocarcinoma, adenoid cystic carcinoma, and carcinoma in pleomorphic adenoma. It is characteristic that PLGA has variety of morphological configurations, such as lobular patterns, papillary or papillary-cystic, cribriform patterns and ductlike structures.

Immunohistochemical findings support the differential diagnosis of PLGA. GFAP, S100 protein, and SMA are able to support the diagnosis, but these findings are not specific (Castle et al. 1999). Among 36 PLGAs of the parotid gland reported, S-100 protein, cytokeratin, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA) and GFAP tended to be positive (Table 1). However, the results of immunohistochemical examination need further accumulation of data because the immunohistochemical investigations to PLGA of the parotid gland are rare.

**Treatment and prognosis of PLGA of the parotid gland**

Based on the results that positive or unknown surgical margins correlate with local recurrence of PLGA of the minor salivary glands (Evans and Luna 2000), a wide local excision of the primary lesion has been recommended for the treatment of PLGA. However, the surrounding essential structures, including facial nerves, sometimes make wide resection difficult in parotid neoplasm. Since perineural infiltration occurs frequently in PLGA (Ellis and Auclair 1996), it is assumed that PLGA arising in the parotid gland is not so easy to control. PLGA is a clinically low
### Table 1. PLGA of the parotid gland.

<table>
<thead>
<tr>
<th>cases</th>
<th>age (yr)</th>
<th>gender</th>
<th>size (mm)</th>
<th>genesis</th>
<th>immunohistochemical findings</th>
<th>treatment</th>
<th>outcome</th>
<th>authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>M</td>
<td>20 × 20 × 15</td>
<td>ex PMA</td>
<td>SMA + S-100 + CK + EMA + keratin + CEA + GFAP ± ± vimentin ± MIB-1</td>
<td>ope</td>
<td>12 mo NED</td>
<td>Mark et al. 2)</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>M</td>
<td>50 × 30</td>
<td>ex PMA</td>
<td>+</td>
<td>ope, RT</td>
<td>18 mo NED</td>
<td>George et al. 3)</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>F</td>
<td>20 × 16 × 10</td>
<td>de novo</td>
<td>+ + + ± ± −</td>
<td>ope, RT</td>
<td>30 mo NED</td>
<td>Miliauskas et al. 4)</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>25 × 20</td>
<td>ex PMA</td>
<td>+ + +</td>
<td>ope</td>
<td>9 mo NED</td>
<td>Mark et al. 5)</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>F</td>
<td>60 × 20</td>
<td>de novo</td>
<td>± ±</td>
<td>ope</td>
<td>60 mo LR</td>
<td>Ritland et al. 6)</td>
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<tr>
<td>6-27</td>
<td>58.8</td>
<td>1 : 7(M : F)</td>
<td>8~100</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
<td>4/14 LR</td>
<td>Kemp et al. 7)</td>
</tr>
<tr>
<td>28</td>
<td>54</td>
<td>F</td>
<td>30</td>
<td>de novo</td>
<td>+</td>
<td>ope, RT</td>
<td>1 y LR</td>
<td>Merchant et al. 8)</td>
</tr>
<tr>
<td>29</td>
<td>69</td>
<td>F</td>
<td>40 × 35</td>
<td>de novo</td>
<td>+ +</td>
<td>ope, RT</td>
<td>2 y NED</td>
<td>Puxeddu et al. 9)</td>
</tr>
<tr>
<td>30</td>
<td>65</td>
<td>F</td>
<td>?</td>
<td>no data</td>
<td>no data</td>
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<td>no data</td>
<td>Gibbons et al. 10)</td>
</tr>
<tr>
<td>31</td>
<td>66</td>
<td>M</td>
<td>?</td>
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<td>no data</td>
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<td>no data</td>
<td>&quot; &quot;</td>
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<tr>
<td>32</td>
<td>65</td>
<td>F</td>
<td>?</td>
<td>de novo</td>
<td>+ + + + + − − +</td>
<td>no data</td>
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<td>Tamiolakis et al. 11)</td>
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<tr>
<td>33</td>
<td>79</td>
<td>M</td>
<td>25</td>
<td>de novo</td>
<td>− +</td>
<td>− + ± ± ope</td>
<td>14 mo NED</td>
<td>Nagao et al. 12)</td>
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<tr>
<td>34</td>
<td>65</td>
<td>M</td>
<td>30</td>
<td>de novo</td>
<td>−  +</td>
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<td>46 mo LR</td>
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<td>35</td>
<td>52</td>
<td>F</td>
<td>30</td>
<td>de novo</td>
<td>− + + + + + + + ± ± ope</td>
<td>0pe, RT</td>
<td>50 mo NED</td>
<td>case 1</td>
</tr>
<tr>
<td>36</td>
<td>55</td>
<td>F</td>
<td>40</td>
<td>ex PMA</td>
<td>− + + + + + + ± ± ope</td>
<td>① ope</td>
<td>6 y LR</td>
<td>case 2</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>① ope</td>
<td>33 mo NED</td>
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</tbody>
</table>

CEA, carcinoembryonic antigen; GFAP, glial fibrillary acidic protein; CK, cytokeratin; DM, distant metastasis; EMA, epithelial membrane antigen; ex PMA, ex pleomorphic adenoma; LR, local recurrence; mo, month(s); NED, no evidence of disease; ope, operation; RT, radiotherapy; SMA, smooth muscle actin; S-100, S-100 protein; y, year(s); +, positive; ±, slightly or partially positive; −, negative; ①, initial treatment; ②, second treatment.
grade malignancy, therefore resection of the facial nerve might be unacceptable. The efficacy and significance of radiotherapy for PLGA have not been proven to date. The previous literature of PLGA of the parotid gland showed that cases showing a negative surgical margin do not develop local recurrence (Table 1). However, the follow-up periods of the cases showing disease free survival were 50 months or less. In case 5, 34 and 36 (Table 1), local recurrence occurred 60, 46 and 72 months after surgery, respectively. Since PLGA grows slowly, long term follow-up for 5 years or more is necessary to determine the prognosis of the neoplasm. Among seven cases receiving postoperative radiotherapy, only one case of local recurrence 11 years after the treatment was reported. Therefore, postoperative radiotherapy carries the potential to control PLGA much longer, though the risk of local recurrence is not completely excluded.

**CONCLUSION**

In conclusion, PLGA of the parotid gland is a rare disease. We reported two additional cases of PLGA of the parotid gland. In addition, we summarized the immunohistological and clinical features of reported cases of PLGA of the parotid gland. Immunohistological findings of PLGA of the parotid gland were essentially same as PLGA of the minor salivary gland. The treatment for the primary lesion will be very important because the local recurrence was observed in the 8 of 33 reported cases of PLGA of the parotid gland. The presence of the facial nerve in the parotid gland often makes wide resection of the primary lesion difficult. Because the radiotherapy was conducted in the several cases of PLGA of the parotid gland, further assessment will be needed about the effectiveness of postoperative radiotherapy for the treatment of the primary lesion.

**References**


