Case Report

Primary ductal adenocarcinoma of the lacrimal sac: the first reported case

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Abstract: Primary lacrimal sac tumor is extremely rare, and moreover, glandular tumor is exceptional. Herein, we described the first documented case of primary ductal adenocarcinoma of the lacrimal sac. A 79-year-old Japanese female presented with persistent swelling of her left lower eyelid. Computed tomography demonstrated an irregular-shaped tumor involving the left lacrimal sac, lower eyelid, sinonasal tract, and internal side of the left orbit. Biopsy from the eyelid revealed a poorly differentiated adenocarcinoma. Histopathological study of the resected lacrimal sac tumor revealed an infiltrative neoplastic growth that was composed of cribriform structures with comedonecrosis. The neoplastic cells had relatively rich granular eosinophilic cytoplasm and large round to oval nuclei containing conspicuous nucleoli. The left cervical lymph nodes had metastatic carcinoma. Immunohistochemically, the neoplastic cells were diffusely positive for gross cystic disease fluid protein-15 and androgen receptor. Moreover, mammalian target of rapamycin (mTOR), 4E-BP1, and p4E-BP1 were expressed. According to these results, an ultimate diagnosis of primary ductal adenocarcinoma of the lacrimal sac was made. Only 9 cases of primary lacrimal sac adenocarcinoma have been reported, and this is the first reported case of ductal adenocarcinoma of the lacrimal sac. Ductal adenocarcinoma of the salivary gland shows an aggressive clinical course, and the present case had multiple cervical lymph node metastases. This report is the first to demonstrate that mTOR pathway proteins, which are central proteins involved in carcinogenesis, are activated in ductal adenocarcinoma. Therefore, mTOR inhibitor may be a potential candidate for treatment of this highly aggressive carcinoma.

Keywords: Ductal adenocarcinoma, lacrimal sac, mTOR pathway

Introduction

Lacrimal sac is the closed upper end of the nasolacrimal duct, and has a fibro-elastic wall lined internally by mucosa that is continuous with the conjunctiva through the lacrimal canaliculi and with the nasal mucosa through the nasolacrimal duct. Primary lacrimal sac tumor is extremely rare, and approximately 400 cases have been reported in the literature [1-4]. About 75% of the primary lacrimal gland tumor is of epithelial origin, and the remaining portion is a non-epithelial tumor [3]. Most of the epithelial tumor of the lacrimal sac is a squamous cell lesion [4], and the presence of glandular tumor is exceptional [3, 4]. Moreover, adenocarcinoma is extremely rare in the lacrimal sac [3, 4]. Herein, we describe the first documented case of ductal adenocarcinoma of the lacrimal sac and review the clinicopathological features of adenocarcinoma of the lacrimal sac.

Case report

A 79-year-old Japanese female without clinical history of salivary gland or breast tumor presented with persistent swelling of her left lower eyelid for approximately 8 months. Computed tomography demonstrated an irregular-shaped tumorous lesion involving the left lacrimal sac, lower eyelid, sinonasal tract, and internal side of the left orbit, which resulted in compression of the eyeball to the external side (Figure 1). Swelling of the left cervical lymph nodes was also observed. Histopathological examination of the biopsy from the lower eyelid revealed a poorly differentiated adenocarcinoma. Subsequently, total resection of the lacrimal sac tumor
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Immunohistochemical analyses were performed using an Autostainer (Ventana) by the same method as previously reported [5, 6]. Table 1 summarizes the immunohistochemical results of the present case. The neoplastic cells were diffusely positive for cytokeratin 7 and gross cystic disease fluid protein (GCDFP)-15 (Figure 3A). Androgen receptor was also diffusely expressed (Figure 3B). Overexpression of HER2/neu protein was not observed. Ki-67 labeling index was 23.5%.

In addition, mammalian target of rapamycin (mTOR), 4E-BP1, and phosphorylated 4E-BP1 (p4E-BP1) were expressed in the neoplastic cells (Figure 3C).

The immunohistochemical characteristics of the metastatic carcinoma in the lymph nodes were identical to those of the primary site.

According to these results, an ultimate diagnosis of primary ductal adenocarcinoma of the lacrimal sac with cervical lymph node metastases was made.

Discussion

In this report, we described the first documented case of primary ductal adenocarcinoma of the lacrimal sac. Ductal adenocarcinoma is a relatively rare malignant tumor that mainly occurs in the salivary gland, especially in the parotid gland, which represents approximately 9% of salivary malignancies, and is referred to as salivary duct carcinoma (SDC) [7]. This type of tumor is also reported in the lacrimal [8, 9] and minor salivary glands [7, 10]. SDC is characterized histopathologically by the presence of a cribriform growth pattern with comedonecrosis, which is composed of neoplastic cells containing rich eosinophilic granular cytoplasm and large pleomorphic nuclei with conspicuous nucleoli, and resembles ductal carcinoma of the breast [7]. Positive immunoreactivity for GCDFP-15 and AR is characteristic, and moreover, most SDC show positive membranous staining for HER2/neu protein [7, 10, 11]. The histopathological features of the present case corresponded to SDC because typical cribriform growth with comedonecrosis, which was composed of neoplastic cells containing rich granular eosinophilic cytoplasm and large round to oval nuclei. Poorly differentiated area comprising of small-sized glands, cords or single cells as seen in the present case can be
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Figure 2. Histopathological features of the lacrimal sac tumor. A: Cribriform growth of the neoplastic cells with or without comedonecrosis. HE, x 40. B: The neoplastic cells have relatively rich granular eosinophilic cytoplasm and large round to oval nuclei containing conspicuous nucleoli. HE, x 200. C: Poorly differentiated adenocarcinoma component demonstrating small-sized glands, cord, or single cell growth of neoplastic cells. HE, x 200. D: Histiocytoid cells are also observed. HE, x 400. E: Lymphatic invasion is prominent, and perineural invasion is also noted (inset). HE, x 200.

Table 1. Summary of immunohistochemical results of the lacrimal sac tumor

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin (AE1/AE3)</td>
<td>DAKO</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>Novocastra</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 20</td>
<td>Novocastra</td>
<td>-</td>
</tr>
<tr>
<td>Epithelial membrane antigen</td>
<td>Novocastra</td>
<td>+</td>
</tr>
<tr>
<td>Gross cystic disease fluid protein-15</td>
<td>Novocastra</td>
<td>+</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Novocastra</td>
<td>+</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Novocastra</td>
<td>-</td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td>DAKO</td>
<td>-</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>DAKO</td>
<td>-</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Novocastra</td>
<td>-</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>DAKO</td>
<td>-</td>
</tr>
<tr>
<td>Ki-67 labeling index (%)</td>
<td>DAKO</td>
<td>23.5</td>
</tr>
<tr>
<td>mTOR</td>
<td>Cell Signaling</td>
<td>+</td>
</tr>
<tr>
<td>4E-BP1</td>
<td>Cell Signaling</td>
<td>+</td>
</tr>
<tr>
<td>p4E-BP1</td>
<td>Cell Signaling</td>
<td>+</td>
</tr>
</tbody>
</table>

present in SDC [7, 12]. Moreover, the neoplastic cells were diffusely immunopositive for GCDFP-15 and AR although overexpression of HER2/neu was not observed in the present case. The lack of HER2/neu overexpression was reported in one of 15 SDC cases described by Skálová et al. [11], and Jaehne et al. documented that 18 of 34 (52.9%) cases of SDC were HER2/neu-negative [10]. Therefore, an ultimate diagnosis of primary ductal adenocarcinoma of the lacrimal sac was made with consideration of no past history of salivary gland or breast tumor.

In addition, histiocytoid cells were observed in the present case. Therefore, primary signet-ring cell/histiocytoid carcinoma (PSRCHC) of the eyelid must be included in the differential diagnostic consideration [13]. PSRCHC is characterized histopathologically by the presence of neoplastic signet-ring cells or histiocytoid cells arranged in an “Indian file” between collagen bundles [13]. Immunohistochemically, the neoplastic cells express GCDFP-15, but are negative for HER2/neu [13, 14]. However, cribriform growth with comedonecrosis, which is a characteristic feature of ductal adenocarcinoma, is not present in PSRCHC.

Primary adenocarcinoma of the lacrimal sac is extremely rare. Only 9 cases of adenocarcinoma and 7 cases of oncocytic adenocarcinoma have been reported in the literature [2-4, 15-19]. Our analysis revealed that primary adenocarcinoma of the lacrimal sac predominantly affects middle-aged to elderly males, and a his-
The pathological characteristic of this type of tumor is the presence of mucin production [2, 3, 15]. Only one case of primary adenocarcinoma ex pleomorphic adenoma of the lacrimal sac has been reported [15]. Oncocytic adenocarcinoma also mainly occurs in the elderly [3, 17], and has been reported to arise from recurrent oncocytoma [17].

A possible origin of lacrimal sac adenocarcinoma is thought to be the seromucinous gland in the lacrimal sac [3]. Pe’er et al. analyzed non-neoplastic lacrimal sac specimens and found that mixed glands with serous and mucinous units, similar to salivary glands, were present in the lacrimal sac [3]. Salivary gland type neoplasms, such as adenoid cystic carcinoma, mucoepidermoid carcinoma, and pleomorphic adenoma, have been documented in the lacrimal sac [1, 3, 4, 15], and these tumors may arise from the seromucinous glands present in the lacrimal sac. Thus, ductal adenocarcinoma of the lacrimal sac may also arise from these glands.

Figure 3. Immunohistochemical features of the lacrimal sac tumor. A: Gross cystic disease fluid protein-15 is diffusely expressed. x 200. B: Androgen receptor is also diffusely expressed. x 200. C: The neoplastic cells are diffusely positive for mTOR, 4E-BP1, and p4E-BP1. x 200.
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SDC is one of the most aggressive carcinomas of the salivary gland. A review of 104 cases of SDC concluded that 33% developed local recurrence and 46% showed distant metastases [20]. Moreover, ductal adenocarcinoma of the minor salivary and lacrimal glands also shows an aggressive clinical course [8-10]. The present case had multiple cervical lymph node metastases, therefore, ductal adenocarcinoma of the lacrimal sac also shows an aggressive clinical course.

In addition, this report is the first to analyze the expression profiles of mTOR pathway proteins in ductal adenocarcinoma. mTOR is a serine/threonine kinase that regulates cell growth and metabolism, and is a central protein involved in carcinogenesis [21]. mTOR phosphorylates 4E-BP1, and then p4E-BP1 leads to cell cycle progression, cell proliferation, and angiogenesis [21]. Activation of mTOR and its regulatory proteins has been reported in various types of tumors [22-25]. Therefore, mTOR is thought to be one of the most promising therapeutic targets in various types of carcinomas, and it has been demonstrated that mTOR inhibitors prolonged survival in some types of carcinomas [26]. The present study clearly demonstrated that mTOR pathway proteins were activated in ductal adenocarcinoma of the lacrimal sac. Therefore, mTOR inhibitor may be a potential candidate for treatment of this highly aggressive carcinoma.

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References

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