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Polymorphous Low-Grade Adenocarcinoma Arising at the Retromolar Region: A Rare Case of High-Grade Malignancy

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Polymorphous low-grade adenocarcinoma (PLGA) is an entity under the subclassification of adenocarcinoma from salivary glands. We report here a rare case of PLGA with suspected metastases to a regional lymph node and the liver, confirmed by magnetic resonance imaging and computed tomography. An 88-year-old Japanese woman complaining of pain in the left mandible, specifically in the gingiva upon swallowing, was referred to our clinical department in July 2003. The pain in the left mandibular gingiva had been noted 10 months before the first medical examination. Oral examination revealed a 38 × 30 mm mass forming from the left retromolar region to the glossopalatal arch with ulcer. An incisional biopsy of the mass revealed PLGA. Histopathologically, tumor cells presenting mild atypia showed tubular and cribriform structures. Immunohistochemically, the Ki-67 labeling index showed 31% suggesting a potential high-grade malignancy of tumor cells.

Key words: high-grade malignancy; immunohistochemistry; metastasis; polymorphous low-grade adenocarcinoma

Polymorphous low-grade adenocarcinoma (PLGA) is an uncommon tumor that usually affects the minor salivary gland. PLGA was described by Freedman (1983) under the name of lobular carcinoma, and by Batsakis and others (1983) as terminal duct carcinoma. Evans and Batsakis (1984) eventually coined the term PLGA. PLGA is characterized by infiltrative growth, morphologic diversity and cytologic uniformity. PLGA usually shows several overlapping histological patterns with pleomorphic adenoma (PA) and adenoid cystic carcinoma (ACC). PA is benign, and its architectural patterns vary, for example, in ducts, strands or sheets. PA has myxochondroid stromal features. The cytologic appearance of PA is uniform without atypia. It is difficult to distinguish between PA and PLGA, but PA is not infiltrative and does not show neurotropism. On the other hand, ACC is malignant and infiltrative, having a tendency toward neural invasion. ACC has various morphologic patterns that are identified as cribriform, solid or tubular. The clinicopathological features of PLGA overlap PA and ACC and that may result in a diagnostic pitfall. The malignancy of PLGA is usually low, and metastases to regional lymph nodes and distant areas

Abbreviations: ACC, adenoid cystic carcinoma; CEA, carcinoembryonic antigen; Cox-2, cyclooxygenase 2; CT, computed tomography; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance image; PA, pleomorphic adenoma; PLGA, polymorphous low-grade adenocarcinoma; SCC, squamous cell carcinoma; a-SMA, alpha smooth muscle actin; VEGF, vascular endothelial growth factor

are uncommon. Local recurrence rates of PLGA range from 10% to 20% and regional metastases are up to 10% on review articles (Gnepp et al., 1988; Vincent et al., 1994). Nevertheless, three histologically confirmed cases of distant metastases from PLGA have been reported (Tanaka et al., 1995; Thomas et al., 1995; Hannen et al., 2000). We report here a rare case of PLGA that occurred in the retromolar region, suspecting metastases in the regional lymph node and liver by computed tomography and echography. In addition, we summarize immunohistochemistry and examine a potential high-grade malignancy of tumor cells.

Patient Report

Patient

An 88-year-old Japanese woman was referred to our clinic at Tottori University Hospital in July 2003. She complained of a pain in the left mandibular gingiva upon swallowing. The pain was noted 10 months before her first medical examination. Oral examination revealed a 38 × 30 mm mass and a 10 mm ulcer at the left retromolar region, the palatoglossal arch and the left tonsil region (Fig. 1). T1-weighted magnetic resonance image (MRI) revealed an unclear image of a mass in the left retromolar region (Fig. 2). Echography revealed a metastasis to the left submandibular lymph node. She also suffered from hypertension and type C hepatitis. Laboratory data showed high levels of AFP (13.4 ng/mL) and CA19-9 (71.8 U/mL), but PIVKA-II was 34 mAU/mL and was within normal limits. A computed tomography (CT) scan revealed a uniform low absorption lesion, 5 cm in diameter, in S5 region of the liver, suggesting liver metastasis (Fig. 3). Specimens of the retromolar region were obtained by incisional biopsy.

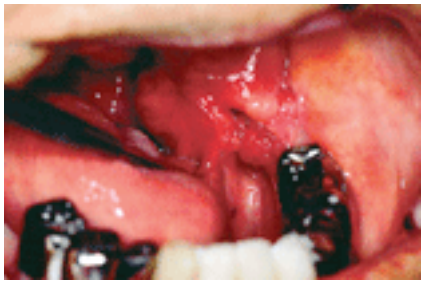

Fig. 1. Clinical findings of polymorphous low-grade adenocarcinoma (PLGA) in the left retromolar region.

Microscopic features of the tumor

Incisional biopsy was performed. After being fixed in 10% buffered formalin for a day, the specimens were embedded in paraffin, and cut into 4- to 5-μm thick sections, then stained with hematoxylin and eosin. The tumor was seen just under the mucosa and had no capsular element. The tumor cells showed mainly tubular and cribriform patterns and consisted of isomorphic epithelial cells having round to oval nuclei with

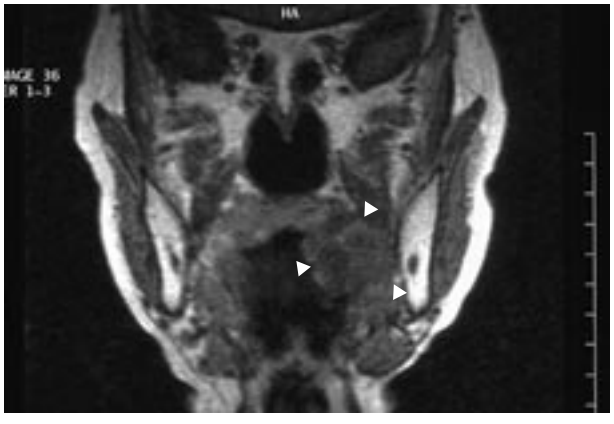

Fig. 2. T1-weighted magnetic resonance image (MRI) shows an unclear low signal in the left retromolar region.

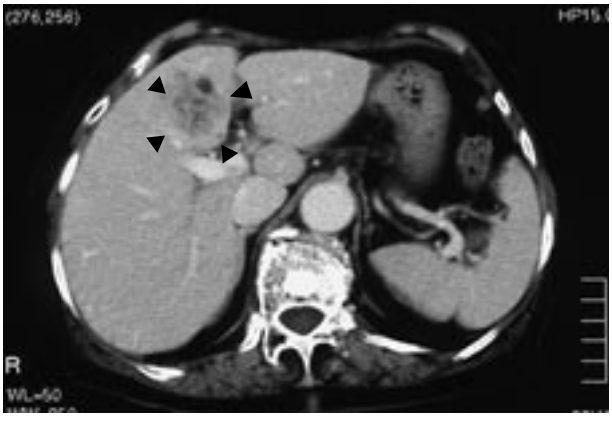

Fig. 3. An enhanced computed tomography (CT) scan shows a 5-cm space occupying in S5 region of the liver.

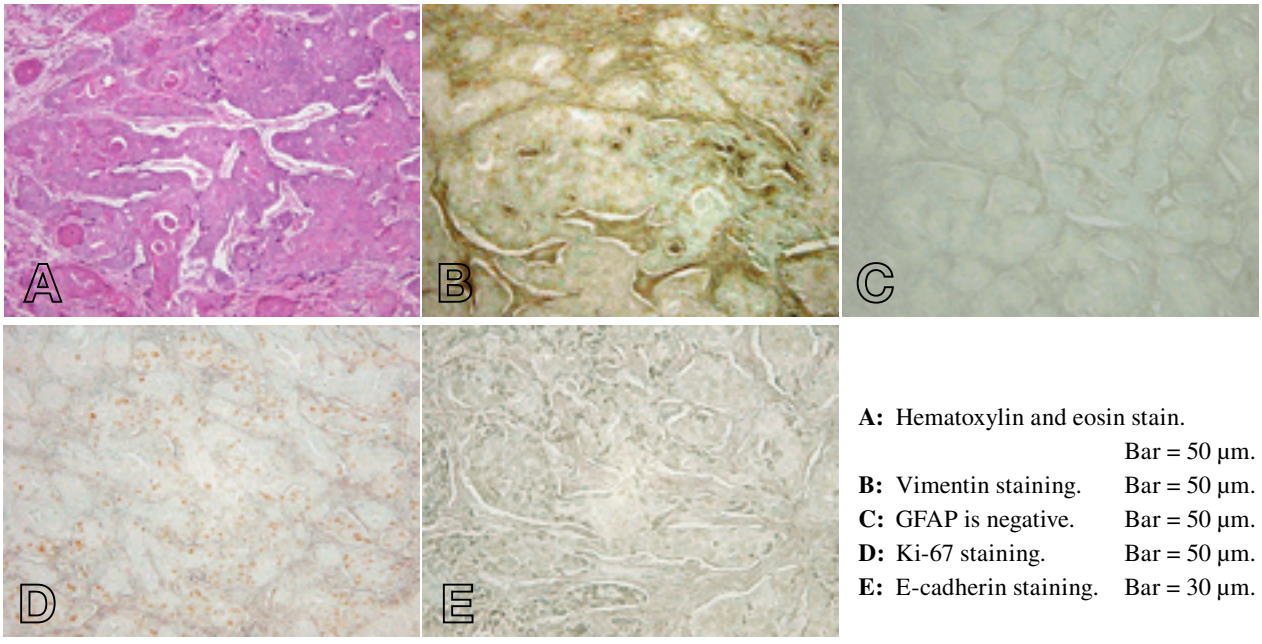

Fig. 4. Histopathological and immunohistochemical findings of polymorphous low-grade adenocarcinoma (PLGA).

non-promiment nucleoli. Mitotic features were rare. Necrotic areas and perineural and vascular invasion were not observed. The tumor stroma showed hyalinization and myxoid changes with focal lymphocyte infiltration (Fig. 4A).

Immunohistochemistry

The paraffin embedded tissue sections were deparaffinized, and sections were blocked with endogenous peroxidase with 0.3% H_2O_2/methanol. They were then incubated at 4˚C overnight with the following antibodies: cytokeratin (AE1/AE3), vimentin, S-100 protein, carcinoembryonic antigen (CEA), alpha smooth muscle actin (α-SMA), glial fibrillary acidic protein (GFAP), Ki-67, E-cadherin, cyclooxygenase 2 (Cox-2), p53 and vascular endothelial growth factor (VEGF) (Table 1). Antigens reacting with each antibody were amplified using the streptavidin-biotin-peroxidase complex method.

Table 1. A summary of the immunostaining of PLGA

Antibody	Source	Dilution	PLGA
Cytokeratin (AE1/AE3)	Nichirei (Tokyo, Japan)	× 1	+
Vimentin	Nichirei (Tokyo, Japan)	× 1	+
S-100 protein	Nichirei (Tokyo, Japan)	× 1	+
Carcinoembryonic antigen (CEA)	Nichirei (Tokyo, Japan)	× 1	Partially +
Alpha smooth muscle actin (α-SMA)	Dako Japan (Kyoto, Japan)	× 50	–
Glial fibrillary acidic protein (GFAP)	Dako Japan (Kyoto, Japan)	× 50	–
Ki-67	Dako Japan (Kyoto, Japan)	× 50	+
E-cadherin	Zymed Laboratories (San Francisco, CA)	× 1	Weak +
Cyclooxygenase 2 (Cox-2)	Cyman Chemical (Ann Arbor, MI)	× 250	–
p53	Dako Japan (Kyoto, Japan)	× 50	–
Vascular endotherial growth factor (VEGF)	Santa Cruz Biotechnolog (Santa Cruz, CA)	× 150	–

+, positive staining; –, negative staining; PLGA, polymorphous low-grade adenocarcinoma.

The tumor was positive for AE1/AE3, vimentin and S-100 protein. CEA was partially positive. Expressions of VEGF, p53, α-SMA and GFAP were not found (Figs. 4B and C). The immunoreactivity of cell adhesion molecular E-cadherin was low. The Ki-67 labeling index was 31.3% (Figs. 4D and E, Table 1). We diagnosed PLGA by histopathology and immunohistochemistry.

Treatment

Our patient underwent two runs of chemotherapy, CDDP (40 mg/m^2)-5-FU (200 mg/m^2) by intra-arterial infusion and external X-ray radiation (6 MV, 2 Gy/fraction/day, total 50 Gy). We injected the agents into the left lingual and maxillary arteries by half doses. Through this treatment, the CT and MRI findings showed a complete response in the primary lesion. Also, the space-occupying lesion of the liver was reduced, so she underwent hepatic arterial infusion chemotherapy with CDDP (20 mg/m^2) and 5-FU (610 mg/m^2) via an implantation port system. Further three courses of chemotherapy were given every week. Although the space-occupying lesion of the liver could still be visualized by CT scan at 2.7 cm in diameter, she was voluntarily discharged. Six months later, she had an additional biopsy performed on her for swelling in the left retromolar region, upon which she was given a diagnosis of recurrence of PLGA. The histological pattern of the second biopsy specimen was the same as that of the first incisional biopsy, confirming the diagnosis of recurrent PLGA. She did not want to be hospitalized which resulted in her death.

Discussion

Of minor salivary gland tumors, PLGA accounts for 7% to 11% of benign and malignant tumors combined, and for 19% to 26% of malignant tumors, and it is the second most common after mucoepidermoid carcinoma (Waldron et al., 1988; Ellis and Aiclair, 1996). Though PLGA is thought to be an indolent tumor, three cases of PLGA with microscopically confirmed distant metastasis have been reported (Tanaka et al., 1995; Thomas et al., 1995; Hannen et al., 2000).

Microscopically, PLGA shows histopathologic features characteristic of many benign and malignant salivary glands neoplasms, particularly several overlapping histological patterns with pleomorphic adenoma (PA) and adenoid cystic carcinoma (ACC). It is difficult to confirm PLGA only by histopathology, so it is necessary to perform immunohistochemical analysis. To differentiate PLGA from PA immunohistochemically, Curran and others (2001) reported that GFAP can be a reliable adjunct for distinguishing PLGA from PA of minor salivary glands due to the absence of reactivity to GFAP in the majority of PLGA cases. Actually, GFAP was negative in our case. Also, Darling and others (2002) reported that vimentin may be the sole marker allowing a distinction between PLGA and ACC due to the presence of reactivity to vimentin in the majority of PLGA cases. In our case, vimentin was positive. With the above-mentioned techniques, we determined the present case to be PLGA.

Generally, PLGA with a predominantly papillary growth pattern has a worse clinical outcome than in this case (Mitchell et al., 1989). But Evans and Luna (2000) reported that papillary areas of more than the focal extent were associated with cervical lymph-node metastasis to a statistically significant degree, while this was not true of local recurrence and distant metastasis. In our case, tumor growth showed mainly tubular and cribriform patterns. Yet the Ki-67 labeling index, a cell proliferation marker, was 31.3% on the first incisional biopsy. In previous studies, Simpson et al. (2002) reported two cases of PLGA with transformation to high-grade carcinoma, and found that the low-grade areas with the Ki-67 labeling index of 2% and 3% were typical, in stark contrast to 38% and 30% in the high-grade elements. E-cadherin was examined in our case. The cell adhesion molecular E-cadherin expression was low. Because of this, we suspected that the pres-

ent case was proof of a high-grade change, since our patient eventually had lymph-node and liver metastases, but those metastasized lesions remained bioptically unproven.

We performed other immunohistochemical analyses to confirm our results. To our knowledge, Cox-2 for PLGA had never been immunohistochemically examined previously. Shibata and others (2005) reported that Cox-2 was noted in the squamous cell carcinomas (SCCs) preceded by dysplasia, but that it was not noted in SCCs not preceded by dysplasias. Therefore, Cox-2 plays some role in the early stages of carcinogenesis of SCCs. In our case, the Ki-67 labeling index was high, and the tumor showed high-grade malignancy. We thought that Cox-2 participates in the change from low-grade to high-grade malignancy in the malignant salivary gland tumors. We tried to analyze Cox-2 in this case immunohistochemically, but the result was negative. It is necessary to examine the result furthermore in the future.

PLGA has low-grade malignancy. In treating PLGA surgically, PLGA is locally excised in a wide fashion including the invaded surgical margins. This procedure seems acceptable after full evaluation of the surgical margins and when followed by radiation therapy (Vincent et al., 1994; Gonzalez-Garcia et al., 2005). But there is no evidence that indicates any benefit from postoperative radiation or adjuvant chemotherapy, although both modalities have been used (Ellis and Aiclair, 1996). PLGA is indolent in many cases, but there is a type of high-grade malignancy that metastasizes to other organs. In our case, we could not excise the tumor because the patient being at an advanced age did not wish to be surgically managed. After PLGA was adopted to the subclassification of adenocarcinoma by the WHO (1991), review articles on PLGA of high-grade malignancy have been reported. We need to examine more cases of PLGA for further considerations.

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