Salivary duct carcinoma in the mandible: a case report

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Salivary duct carcinoma (SDC) is a distinctive and aggressive neoplasm. The most frequent site of origin is the parotid gland, followed by the submandibular gland. SDC originating in the minor salivary glands, particularly in the ectopic glands within the mandible, is extremely rare. We describe a 62-year-old man with SDC in the mandible, who presented with a painless lump in the right submandibular region (later identified as lymph node metastasis) and ipsilateral mental nerve palsy. Histologic examination after ablative surgery revealed SDC originating in the mandible and cervical nodal metastases spreading to levels I-III. The patient remains alive 59 months after presentation as a result of postoperative full-dose irradiation and regular intensive chemotherapy using TXT, 5-FU, and CDDP. However, the patient has local recurrence and distant metastases to the lung and brain. In this report, we also discuss the specific diagnostic criteria and developmental theories of intraosseous salivary gland tumors. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:e41-e46)

Salivary duct carcinoma (SDC) is an uncommon pathologically distinct entity characterized by its morphologic resemblance to ductal carcinoma of the breast and highly aggressive behavior. It was initially described by Kleinsasser et al.1 in 1968 and was first incorporated into the second version of the World Health Organization classification of salivary gland tumors2 in 1991. This neoplasm has been reported to exhibit a male predominance of 4:1 to 8:1 and occurs at a mean age of 60-66 years.3–6 Typical presenting symptoms include a painful or painless rapidly enlarging firm mass, and the condition is frequently (29%-42%) associated with facial nerve palsy or paralysis.5,7 The parotid gland is most frequently involved in SDC, followed by the submandibular gland.3,5,7 To the best of our knowledge, only 25 cases of SDC originating in the intraoral minor salivary glands have been reported in the English-language literature. The most frequent site is the palate (9 cases),1,3,8-12 followed by the buccal mucosa or vestibule (7 cases),3,9,13-15 maxilla (3 cases),16,17 tongue (2 cases),18,19 upper lip (1 case),20 retromolar area (1 case),21 floor of the mouth (1 case),22 and mandible (1 case).23 Two of the three reports of SDC originating in the jaw17,23 included inadequate information regarding the clinical course and biologic behavior of the lesions or did not provide histologic support for the diagnosis.16 Information on SDC originating in the jaw is therefore scarce. In the current report, we describe a new case of mandibular SDC.

CASE REPORT
A 62-year-old Japanese man was referred to us with a painless lump in the right submandibular region and right mental nerve palsy. The lump had enlarged progressively over the previous 6 months, and mental nerve palsy had appeared 2 months beforehand. All of the third molars had been extracted several decades previously, but details of this procedure were unknown. The patient had a medical history of alcoholic hepatitis, but this condition was well controlled at the time he presented to us. The family history was noncontributory. Physical examination revealed soft mobile lymphadenopathy measuring 20 mm in the right submandibular area and diminished sensation on the right side of the mental and lower lip regions. Intraorally, no significant abnormalities of the oral mucosa or teeth were noted. Panoramic radiography revealed no marked radiolucent lesion. Computerized tomography (CT) demonstrated intact mandibular cortical bone and no lesion in the parotid and submandibular glands. Radionuclide imaging revealed uptake of 99mTc in the right submandibular area and diminished sensation on the right side of the mental and lower lip regions. Intraorally, no significant abnormalities of the oral mucosa or teeth were noted. Panoramic radiography revealed no marked radiolucent lesion. Computerized tomography (CT) demonstrated intact mandibular cortical bone and no lesion in the parotid and submandibular glands. Radionuclide imaging revealed uptake of 99mTc in the right mandibular angle and slight uptake of 67Ga in the right submandibular region. These findings suggested either a malignant lesion or osteomyelitis of the mandible. Biopsy was recommended, but the patient did not consent to this. Therefore, the patient was administered antibiotics and followed clinically on the basis of a provisional diagnosis of osteomyelitis. After 5 months, the swelling around the right parotid gland and the masseter muscle had become significant. Panoramic radiography revealed a ground glass–like appearance (Fig. 1), and CT demonstrated an expanding osteolytic lesion at the right mandibular angle (Fig. 2). After obtaining informed consent, biopsy was performed at the right lower retromolar region. Histologic examination revealed a few atypical epi-
the epithelial cells scattered deeply in the submucosal area, separate from the minor salivary glands in the region. Because some of the atypical cells contained mucin, a diagnosis of central mucoepidermoid carcinoma (MEC) was established. The patient underwent right hemimandibulectomy with ipsilateral radical neck dissection. The resected site was reconstructed using a rectus abdominis musculocutaneous flap combined with a titanium mandibular reconstruction plate. Total excision of the tumor was confirmed with definitive microscopic examination; however, radiotherapy (total 61.2 Gy) was performed postoperatively, because multiple cervical nodal metastases were discovered at levels I, II, and III. Distant metastasis appeared in the lung 14 months after the ablative surgery and in the brain after 46 months. Local recurrence was also detected 20 months postoperatively. At the time of writing (59 months after the first examination), the patient remains alive and undergoes regular chemotherapy to control the tumor every 3 months using TXT (100 mg/body, day 1), 5-FU (1,000 mg/body × 5; day 2-6), and CDDP (100 mg/body, day 7). Gamma-knife therapy was performed for the brain metastasis, resulting in reduction of tumor size.

PATHOLOGIC FINDINGS
On gross examination, the tumor was seen to be expanding centrally within the mandible with infiltration partially over the cortical bone into the muscles. The cut surface of the tumor was whitish with yellow granules. The surface of the oral mucosa was smooth with the exception of ulceration caused by the biopsy. The submandibular lesion was well circumscribed and not directly connected to the intraosseous lesion (Fig. 3). Histologic examination revealed that the tumor consisted of solid and cribriform cell nests with ductal structures, and many of these nests showed comedolike central necrosis. Typical cribriform cell nests frequently exhibited the so-called “Roman bridge” pattern. An invasive component resembling infiltrating ductal adenocarcinoma of the breast with irregular cell nests and dense fibrous tissue was observed in some regions of the specimen. Neoplastic cells were large and polygonal with eosinophytic cytoplasm, ovoid hyperchromatic or vesicular nucleus, and prominent nucleoli. These cells showed nuclear pleomorphism and mitotic figures. A few mucous cells positive for periodic acid–Schiff (PAS) and Alcian blue (pH 2.5) were observed (Fig. 4). Tumor invasion into the vessels was seen, as well as perineural infiltration. On immunohistochemical analyses, neoplastic cells were positive for cytokeratin (AE1/AE3 and CAM5.2), androgen receptor protein (AR), and BRST-2 (gross cystic disease fluid protein [GCDFP]-15) (Fig. 5) and negative for smooth muscle actin, S-100 protein, and vimentin. From these findings, the final histologic diagnosis of SDC was made. Many cervical lymph node metastases were evident, extending to level III, with invasion over the capsule. Lymph node metastasis was also suspected for the submandibular lesion (clinically the first mass to arise). The right submandibular gland was intact.

DISCUSSION
Salivary duct carcinoma is characterized pathologically by an intraductal component of dysplastic ductal
Fig. 3. Gross findings of the resected mandible. The oral surface mucosa of the hemimandibular specimen was intact, with the exception of an ulcer caused by the biopsy (top right). The tumor, which was white with yellow granules on the cut surface, occupied the center of the mandible (i-iii). The cortical bone appeared thinned, particularly at the mandibular angle, and the tumor had infiltrated the soft tissue around the mandible (i). The submandibular mass was well circumscribed and not connected to the intraosseous lesion (ii).

Fig. 4. Histologic findings of the tumor. A, The cell nests predominantly exhibited a cribiform pattern with comedolike central necrosis (H&E staining, 100×). B, The so-called “Roman bridge” pattern was seen in cribiform cell nests, suggesting SDC (H&E staining, 200×). C, Invasive components with dense stromal fibrosis were observed in some areas, resembling invasive ductal carcinoma of the breast (H&E staining, 100×). D, A few mucous cells positive for Alcian blue staining were found. Some small cystic or ductal spaces contained mucin (Alcian blue (pH 2.5) staining, 400×).
cells that grow in solid, cribiform, and papillary configurations, often with comedolike central necrosis, and by an invasive component consisting of irregular glands and cords of compressed cells with dense fibrous stroma. Tumor cells are cuboidal and polygonal with eosinophilic cytoplasm and show cytologic features of malignancy, such as cellular and nuclear pleomorphism, nuclear hyperchromatism, and mitotic figures. In the present case, resected specimens clearly revealed that SDC with typical histologic findings had occupied the central part of the mandible. The initial misdiagnosis resulted from the presence of mucous cells, which are often contained in SDC, on the preoperative biopsy.

Salivary gland carcinoma arising centrally in the mandible is extremely rare; this origin is found in only 0.29%-0.37% of cases. Specific criteria to confirm the origin of salivary gland neoplasms within the jaw include: 1) radiographic evidence of an osteolytic lesion; 2) presence of intact cortical bone; 3) no connection between the oral mucosal surface and the lesion; 4) histologic confirmation of salivary gland neoplasm; exclusion of odontogenic tumors; and 5) exclusion of metastasis from any primary lesions. The present case satisfied all of these criteria.

First, osteolytic change was noted in preoperative CT images. The radiographic appearance of a salivary gland tumor arising in the mandible is extremely rare; this origin is found in only 0.29%-0.37% of cases. An incorrect provisional diagnosis of osteomyelitis was established in the present case because radiolucrency of the mandibular canal was very obscure at initial examination. Moreover, the ground glass appearance noticed 6 months later on panoramic radiography was unusual for a central salivary gland tumor. CT showed irregular destruction of the cortical bone, similar to that observed in a case of SDC originating in the maxilla. This characteristic finding may have resulted from the aggressive behavior of the tumor.

Second, the intact cortical bone was revealed radiographically at the first examination. Third, Ide et al. reported a case of sarcomatoid SDC protruding from the retromolar area and extending focally into the pharyngeal wall. In the present case, atypical epithelial cells in the biopsy specimen were scattered deeply in the submucosal area and were far from the oral mucosa and the retromolar minor salivary glands. Fourth, the histologic findings confirmed the neoplasm to be a salivary gland tumor; odontogenic tumor was excluded. And fifth, the symptom first identified, the submandibular lump, was a nodal metastasis. Histologic examination revealed that the submandibular gland, the second most frequent site of SDC, was intact and separated clearly from the submandibular lump. Some researchers have reported carcinomas originating in an ectopic salivary gland within intraparotid lymph nodes or the neck area. The primary site might therefore represent an ectopic salivary gland, with the mandibular lesion being a metastasis. In fact, 2 cases of salivary duct carcinoma of the larynx have been reported. However, in the present case, whole-body imaging failed to identify ectopic salivary gland tumors in any other region. Furthermore, a review of 390 cases with metastatic tumors of the jaw reported by Hirshberg et al. did not identify any cases of salivary gland carcinoma metastatic to the mandible.

Several theories have been proposed to explain the occurrence of primary salivary gland tumors of the jaw: 1) ectopic entrapment of retromolar mucous glands during embryologic development of the jaw; 2) developmentally included remnants of submandibular and sublingual glands within recesses or lacunae of the mandible; 3) submandibular and sublingual glands closely apposed in bony defects or cavities in the lingual cortex of the mandible; and 4) neoplastic or metaplastic transformation of the mucous cells in the epithelial linings of dentigerous cysts or odontogenic epithelium. The last theory is considered to be the most convincing, particularly for central MEC; the

![Fig. 5. Immunohistochemistry. A. The majority of tumor cells exhibited nuclei positive for androgen receptor protein (100×). B. Tumor cells were strongly positive for BRST-2 (GSFP-15) (100×).](image-url)
most frequently reported histologic type (64%-75% of cases)\textsuperscript{5,3,3,4} of primary central salivary gland carcinoma of the mandible. Eversole et al.\textsuperscript{35} reported that 48% of patients with central MEC exhibited either odontogenic cysts or an impacted tooth. Brookstone and Huvos\textsuperscript{25} reported that 30% of central salivary gland tumors of the jaw were associated with either an odontogenic cyst or a previous dental extraction when all histologic subtypes of tumors were included. In our case, the patient had a history of third molar extraction, and histologic examination revealed some mucous cells. Accordingly, as is the case for central MEC, there might be some relationship between the pathogenesis of central SDC and the presence of dentigerous cysts or odontogenic epithelium.

Brookstone and Huvos\textsuperscript{25} proposed a staging system for salivary gland tumors within the mandible. In this system, stage I lesions are located within the undisturbed intact cortical bone and overlying periosteum and show no sign of cortical expansion. Stage II lesions are surrounded by intact cortical bone and show some degree of expansion. Presence of cortical perforation, breakdown of the overlying periosteum, or nodal metastasis is categorized as stage III. Our case was therefore categorized as stage III based on this staging system.

Salivary duct carcinoma originating in the minor salivary glands has been described as less aggressive than that arising in the major salivary glands.\textsuperscript{16} Approximately 22% of SDC originating in the minor salivary glands metastasize to the lymph nodes, as compared with 83% of those arising in the major salivary glands.\textsuperscript{36} In the present case, however, the painless lump in the right submandibular region recognized at the first examination was considered to be a nodal metastasis. Urban et al.\textsuperscript{16} reported a definite case of central SDC involving the cavernous sinus. Accordingly, central SDC might have aggressive characteristics similar to those of ordinary SDC originating in major salivary glands.

Regarding the treatment of SDC, because the tumor grows infiltratively total resection of the tumor with a large safety margin is essential for local control. However, local recurrence has been reported in around 40%-45% of cases.\textsuperscript{5,3,3} This rate was reduced to about 21%-35% with the combination of surgery and radiotherapy.\textsuperscript{5} The rate of distant metastasis is very high (46%-62%), with the most frequent sites being the liver, lung, bone, and brain.\textsuperscript{7} The high mortality rate of SDC is attributed to this propensity to distant metastasis: 5-year survival rate is 11%-30%.\textsuperscript{5,7} and mortality rate is 54%-82%.\textsuperscript{1,5,7,3} The patient reported here developed distant metastases to the lung and the brain in addition to local recurrence, even after an elective surgery, full-dose postoperative irradiation, and regular intensive chemotherapy using TXT, 5-FU, and CDDP. The optimal treatment strategy for patients with SDC, particularly that originating in the jaw, cannot be established until more reports accumulate in the literature.

REFERENCES

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