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## CASE REPORT

# Mucinous adenocarcinoma with neuroendocrine differentiation of the mandibular ramus: report of a case

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**A rare case of mucinous adenocarcinoma with neuroendocrine differentiation of the mandibular ramus is presented. The patient, an 80-year-old man, was referred to our hospital with chief complaint of swelling and pain in the left buccal mucosa. CT and MRI examination showed an osteolytic tumor mass occupying the upper region of the left mandibular ramus. Macroscopically, the excised tumor was a relatively well-defined, solid mass with diffuse bone resorption, measuring 3 cm × 3.2 cm × 3 cm. Microscopical examination showed that the tumor forming glandular structures with abundant mucous production and high cellular atypia. Immunohistochemical studies demonstrated the positive reactivities for pan-keratin, cytokeratin 7, vimentin,α-amylase, α-smooth muscle actin, neuron-specific enolase, glial fibrillary acid protein, calcitonin, and somatostatin in tumor cells. These findings suggested that the tumor was originated from heterotopic or misplaced salivary gland in the mandible.**
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**Keywords:** mandibular ramus; mucinous adenocarcinoma; neuroendocrine differentiation

An 80-year-old Japanese man had noticed paresthesia and continuous pain of the left mental region for the past 1 month. He was referred to our clinic on November 29, 1999 with chief complaint of spontaneous pain of the left buccal region and feeding disturbance. On physical examination, paresthesia was observed in the innervating area of the left mental nerve, and spontaneous pain existed in the left mandibular ramus extending to intraoral region. There was a diffuse swelling in the left upper posterior buccal mucosa. On palpation, an elastic, hard, and thumb-size mass was recognized in the anterior portion of the left mandibular ramus (Fig. 1). Trismus was not observed, and the regional lymph nodes were not palpable. Orthopantomography showed a diffuse bone resorption in the left incisura and inside the left mandibular ramus (Fig. 2). CT scan showed an irregular mass measuring 30 mm × 20 mm and bone resorption in the left mandibular ramus (Fig. 3). Laboratory data were within the normal range. Physical examination of various organs including pancreas and adrenal gland showed no abnormalities. Chest X-ray and $^{67}$Ga and $^{99m}$Tc scintigram also detected no metastatic lesion in those organs. The clinical diagnosis was a malignant tumor of the left mandibular ramus.

A biopsy was performed intraorally, and the lesion was histopathologically diagnosed as mucinous adenocarcinoma. Under general anesthesia, the tumor was excised extraorally with left partial mandibulectomy including the adjacent masseter and medial pterygoid muscles, left upper neck dissection, and mandibular reconstruction with a titanium plate on January 11, 2000 (Fig. 4). The tumor mass was separated from the parotid gland. The cut surface was yellowish-white and mucinous. After 2 months, the patient died of opportunistic infection caused by cryptogenic disease in another hospital. No autopsy was performed.

Microscopically, occasionally floating tumor cells were found in the mucous material with abortive glandular component (Fig. 5a). Partially, tumor nests with solid proliferation were formed by round to oval cells with nuclear atypia (Fig. 5b). Regional lymph node metastasis was found in the left middle submandibular lymph node.

Immunohistochemical study by streptavidin–biotin–peroxidase complex (SABC) method (1) was carried out using antibodies against pan-keratin (1 : 200), cytokeratin 7 (CK7, 1 : 50) and cytokeratin 20 (CK20, 1 : 40; DAKO, Copenhagen, Denmark), epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA) (Pre-diluted; Shandon-Lipshow, Pittsburg, PA) vimentin (1 : 200; Biomeda, Foster, CA), α-smooth muscle actin (α-SMA) (Pre-diluted; Shandon-Lipshow), α-amylase(1 : 100; Sigma Immuno-chemicals, St. Louis, MO), glial fibrillary acid protein (GFAP), neuron-specific enolase (NSE), calcitonin, and somatostatin (Pre-diluted; Shandon-Lipshow).

Consequently, pan-keratin, CK7, EMA, vimentin, CEA, α-SMA, α-amylase, NSE, GFAP, and calcitonin were positive in the tumor cells. Among them, the reaction for

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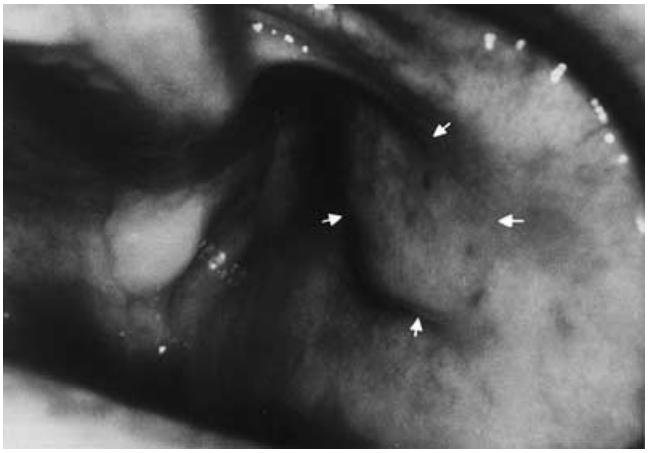

**Figure 1** Intraoral photography showing diffuse swelling of the left buccal mucosa (arrows).

α-amylase was observed in the majority of the tumor cells (Fig. 6a). There were also positive immunoreactivities for pan-keratin, CK7, and EMA in both of the glandular structures with tubular formation and the solid proliferative foci, for vimentin in the solid proliferative foci of the tumor, and for CEA, α-SMA, NSE, GFAP, calcitonin, and somatostatin in a part of glandular, and microcystic structures with tubular formation. Among all of them, the expression of α-SMA was found in abluminal cells of ductular structures of the tumor tissue (Fig. 6b–f). On the basis of these findings, the lesion was finally diagnosed as a mucinos adenocarcinoma with neuroendocrine differentiation.

## Comments

A malignant epithelial neoplasm characterized by abundant mucous production, known as 'mucin-producing adenocarcinoma' (MucAC), commonly occurs in the gastrointestinal tract and occasionally in the breast (2), but is very rare in the head and neck region. The histological types of representative tumors in the head and neck region are MucAC,

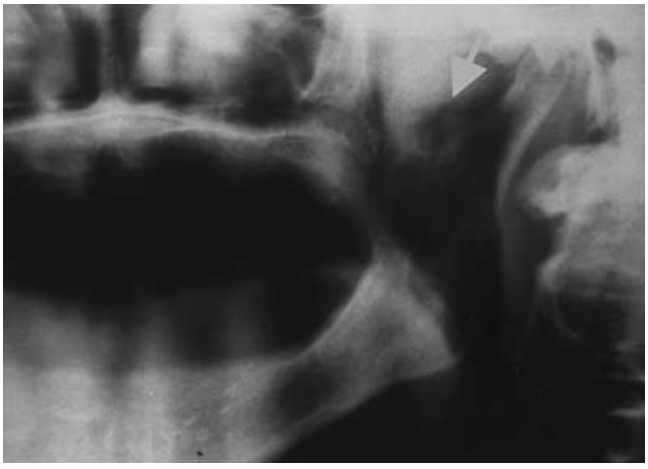

**Figure 2** Orthopantomography showing bone resorption in the left mandibular ramus (arrow).

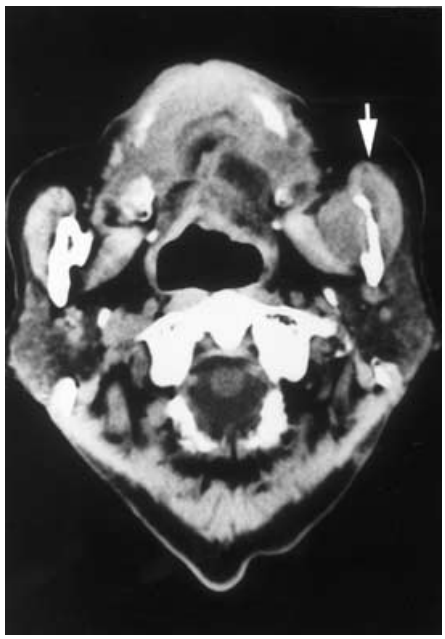

**Figure 3** Computed tomography showing an irregular mass (arrow).

cystadenocarcinoma (papillary cystadenocarcinoma) (3, 4), and mucinous eccrine carcinoma (5). The common characteristics in these tumors are an abundant mucin production and positive reaction for mucicarmine in the histochemical staining. Among them, MucAC and cystadenocarcinoma usually occur in salivary gland (3, 4), and the former occurs occasionally in nasal cavity and paranasal sinuses (6). Mucinous eccrine carcinoma arises most often in the head and neck region, frequently on the eyelids of elderly people (7).

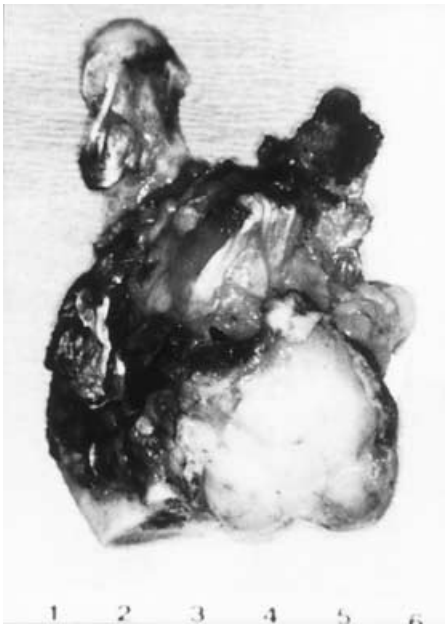


**Figure 4** Macroscopic appearance of the surgical specimen.

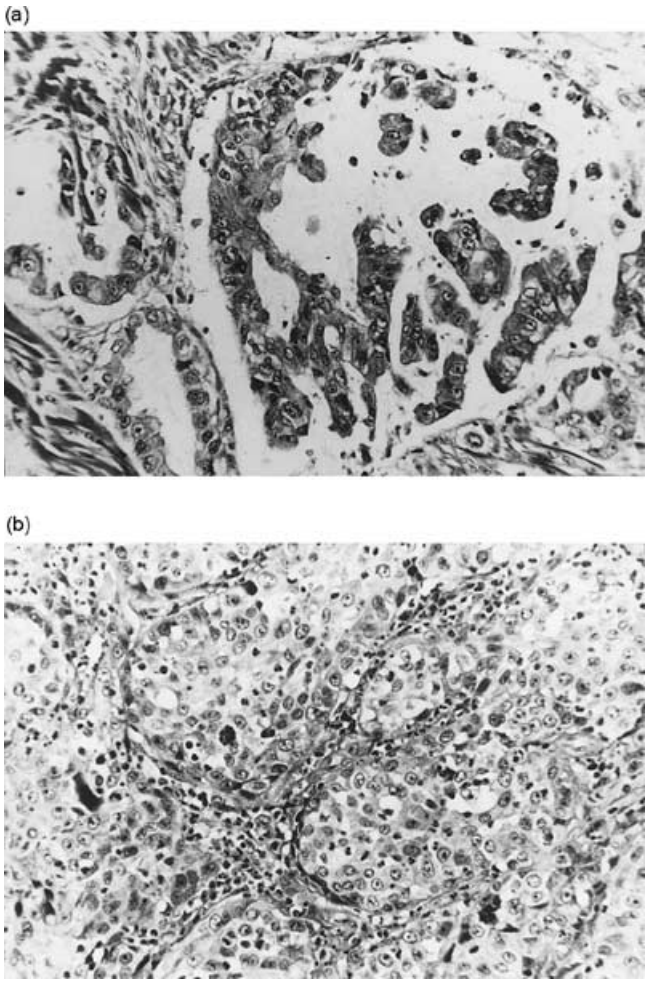


**Figure 5** Photomicrographs of surgical specimen occasionally showing floating tumor cells in the mucinous material with abortive glandular component ((a) H&E, original magnification, ×200). Partly, the tumor foci compatible with undifferentiated carcinoma were present ((b) H&E, original magnification, ×200).

However, there is no previous report of the tumor arising primarily in the mandible.

In the present case, it is feasible that the tumor originated from the intraosseous component from the clinical features and CT and MRI findings. The tumor showed tubular formation with abundant mucin production as the fundamental histological feature. It was also observed that tumor cells were floating in mucous materials in a part of the tumor tissue, but no cystic component was present. From these findings, we speculated that the tumor is analogous to MucAC. In the histological typing of esophageal and gastric tumors and intestinal tumors by the World Health Organization (WHO) (8, 9), it is described that MucAC retains a substantial amount of extracellular mucin (more than 50% of the tumor). According to the description, this tumor can be classified by the growth pattern into two groups; type A, glands lined by a columnar mucous secreting epithelium, together with intestinal mucin, and type B, chains or irregular clusters of cells surrounded by mucins. In our case, the histological diagnosis may correspond to type A; well-differentiated MucAC if the category in the gastric carcinoma is applied.

Reports describing MucAC in the head and neck region are scarce. To date, 10 cases have been found in salivary glands (4–13) and several cases in the nasal cavity and paranasal sinuses (6). In the salivary glands, majority cases arose in the major salivary glands; three parotid, five submandibular, one sublingual, and one palatal minor gland. The criteria in the histological diagnosis of salivary gland MucAC is controversial. In the histological typing of salivary gland tumors by WHO (3), this tumor is described as a tumor in which cuboidal or columnar cells are lining mucus-filled lumens or cysts, and the mucus should occupy over 50% of the tumor without epidermoid and intermediate cells. This description is in close agreement with that by WHO in the gastrointestinal carcinomas (8, 9). However, the histological criteria of this tumor in the salivary gland by Armed Forces Institute of Pathology (AFIP) (4) is rather different from those of WHO. It described this tumor as a rare malignant neoplasm characterized by a large amount of extracellular mucin that contains cords, nests, and solitary epithelial cells. We considered that it resembles type B; poorly differentiated type of gastric MucAC in the description by WHO. On the other hand, AFIP claimed that the microphotographs of WHO showing epithelial lined, mucin-filled cysts histologically would be classified as cystadenocarcinoma. In the description of AFIP, virtually the tumor corresponding to type A of gastric MucAC in WHO is dealt with cystadenocarcinoma in salivary gland. Our unusual mucin-filled and solid tumor resembled those tumors, but no obvious cyst formation was present. From these considerations, we have tentatively diagnosed it as MucAC. More information is needed to understand the histogenesis of this tumor and to determine the precise histological diagnosis.

Immunohistochemical detection has been shown to be useful in the supportive diagnosis of salivary gland tumor. In particular, the expression of myoepithelial cell markers such as CK, vimentin, S-100 protein, α-SMA, and GFAP that characterized most salivary gland tumor. Among all of them, GFAP is almost exclusively found in pleomorphic adenoma. GFAP reactivity is usually limited to myxoid area and absent in cellular region (14). In our case, the tumor cells showed a positive immunoreactions for α-amylase with those myoepithelial cell markers. This fact has important implication in the search for the origin of this tumor. As α-amylase expression is only observed in salivary gland, we considered that the expression of α-amylase in the site except for salivary gland is heterotopic expression.

On the other hand, the tumor cells were demonstrated positive immunoreactions for NSE, calcitonin and somatostatin. From these findings, it is suggested that the tumor has neuroendocrine differentiation. In this case, it can be denied that tumor derived from the diverse neuroendocrine organs, i.e. thyroid, pancreas, adrenal gland and prostate because no demonstrable lesions were found on physical examination of these organs. To date, there is no report of MucAC showing with neuroendocrine differentiation. The pathological significance of these neuroendocrine expressions in the tumor is still unknown.

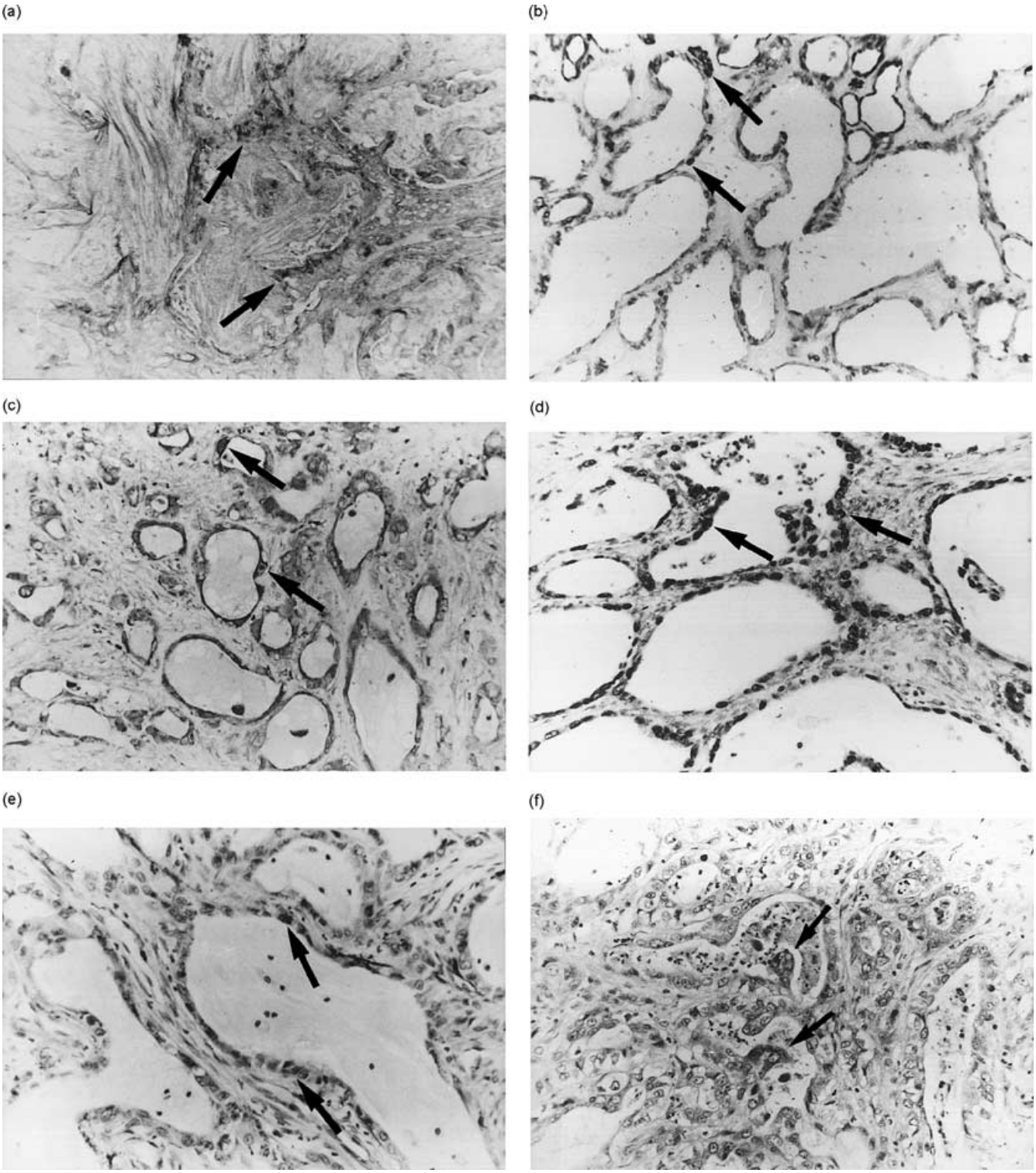


**Figure 6** Immunohistochemical findings of tumor tissue. (a) α-amylase (arrows) stained diffusely in extracellular mucinous material and the secreting side of tumor cells (original magnification, × 200). Positive immunoreactions for (b) pan-keratin (arrows) (c) carcinoembryonic antigen (arrows) and (d) neuron-specific antigen (arrows) in the majority of glandular tumor cells, and (e) α-smooth muscleactin (arrows); and (f) calcitonin (arrows) in some glandular tumor cells (original magnification, ×200).

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