

Large-Cell Undifferentiated Carcinoma of the Submandibular Gland

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Occurrence of large-cell undifferentiated carcinoma in the submandibular gland is uncommon. A 52-year-old man with a 30-mm tumor underwent radical resection of the left submandibular gland together with selective dissection of enlarged ipsilateral cervical nodes followed by postoperative radiotherapy. After histologic examination identified the submandibular gland mass as large-cell undifferentiated carcinoma, selective dissection of enlarged contralateral cervical nodes was performed. The patient showed no evidence of distant metastasis at 24 months after initial treatment.

Key words: large-cell type; submandibular gland; undifferentiated carcinoma

Large-cell undifferentiated carcinoma of major salivary glands is extremely rare accounting for less than 3% of epithelial cancers involving these organs. Most large-cell undifferentiated carcinomas of the salivary gland occur in the parotid. A review of the literature disclosed only a few cases where large-cell undifferentiated carcinoma originated from the submandibular gland. We report such a tumor diagnosed by histology and immunohistochemistry.

Patient Report

A 52-year-old Japanese man noticed a painless left submandibular mass in May 2006. He consulted a clinic where he was diagnosed with a submandibular gland neoplasm, and was referred to our hospital in June 2006. A firm fixed mass with no tenderness was noted in the left submandibular region. Cervical lymphadenopathy was evident in the upper left portion of the neck. Computed tomography (CT) and magnetic resonance imaging

(MRI) demonstrated a tumor with indistinct margins and contrasted enhancement slightly greater than in the submandibular gland, measuring 30 mm in greatest dimension and located in the lower part of the gland. Multiple cervical lymph nodes on the left side showed contrast enhancement (Fig. 1). A malignant neoplasm was strongly suspected. Fine-needle aspiration cytologic examination resulted in a provisional diagnosis of adenocarcinoma versus pleomorphic adenocarcinoma.

The patient underwent radical left submandibular gland resection including wide local excision and selective neck dissection in July 2006. Based on these findings, the tumor was diagnosed as large-cell undifferentiated carcinoma. CT and MRI demonstrated no distant metastasis in the chest or abdomen.

Postoperative radiotherapy was performed with a total dose of 60 Gy over a wide left submandibular and cervical field. After radiotherapy, contralateral cervical lymph nodes began to enlarge gradually. Cytologic malignant metastasis to these nodes was suspected. Accordingly, the

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

patient underwent selective node dissection on the right side of the neck in November 2006. Malignant cells were not found in resected lymph nodes. The patient has shown no signs of recurrence or metastasis over the 24 months following this node dissection.

Pathological Findings

Most of the left submandibular gland had been replaced by a firm tumor measuring 30 mm. The resected tumor was yellow-gray and rubbery (Fig. 2). No necrotic or cystic areas were found. The tumor showed no microscopic invasion of surrounding tissue. Keratinization was not apparent in routinely stained sections (Fig. 3). Tumor cells were arranged in palisades or sheets, and had large, atypical nuclei (Fig. 4). Immunohistochemically, tumor cells showed positive reactions for keratin AE1to3, keratin 7 and epithelial membrane antigen, while showing negative reactions for keratin 20, carbohydrate antigen 19-9, S-100, carcino-embryonic antigen and vimentin. Based on these findings, the tumor was diagnosed as large-cell undifferentiated carcinoma. Metastasis was found in 2 lymph nodes from the upper neck.

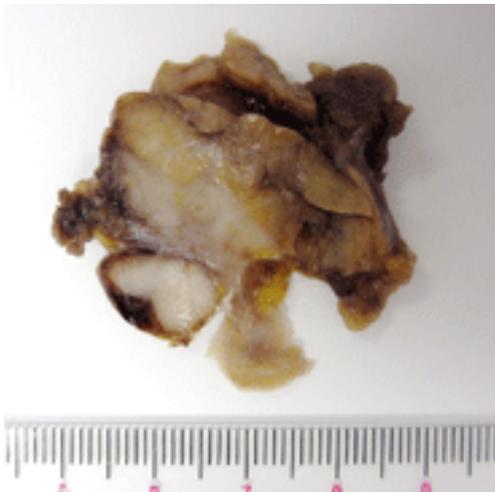


Fig. 2. The resected specimen included a yellow-gray, firm and rubbery tumor.

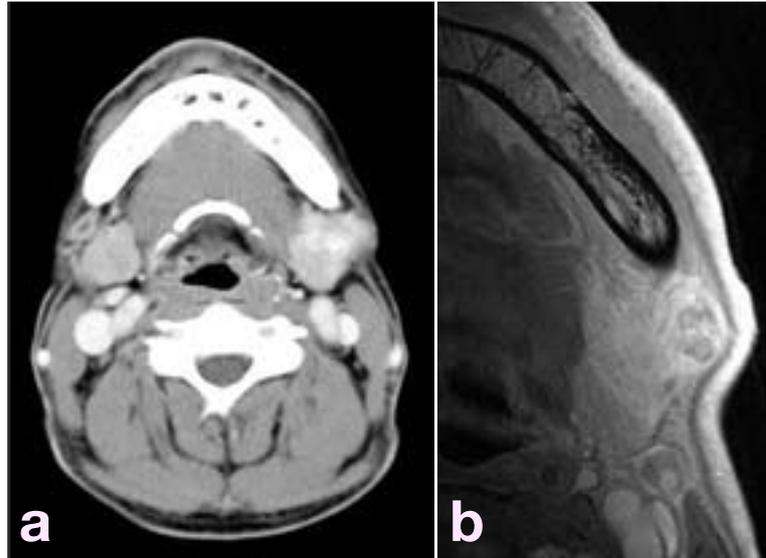


Fig. 1. By CT (a) and MRI (b), a tumor with indistinct margins shows contrast enhancement slightly exceeding that in submandibular gland. The tumor measures 30 mm in maximal dimension and is located in the inferior portion of the gland.

Discussion

Undifferentiated carcinoma of the major salivary glands is uncommon, and reported to account for 1% to 4.1% of epithelial salivary gland neoplasms (Nagao et al., 1982; Wang et al., 2004). Most undifferentiated salivary gland carcinomas have occurred in the parotid. Even so, undifferentiated carcinoma has been reported to account for only 1% to 5.5% of all malignant parotid gland neoplasms (Eneroth, 1964; Patey et al., 1965; Seifert and Donath, 1976; Wang et al., 2004). Little is known about undifferentiated carcinoma of the submandibular gland, and only a few cases have been reported (Wahlberg et al., 2002; Uemaetomari and Ito, 2005; Lin et al., 2006).

Undifferentiated carcinoma of salivary glands is classified as either small- or large-cell type. Small-cell undifferentiated carcinoma apparently is 2 to 3 times more frequent than large-cell undifferentiated carcinoma (Nagao et al., 1982; Hui et al., 1990). The present patient was diagnosed with large-cell undifferentiated carcinoma of the submandibular gland.

The differential diagnosis of large-cell undif-

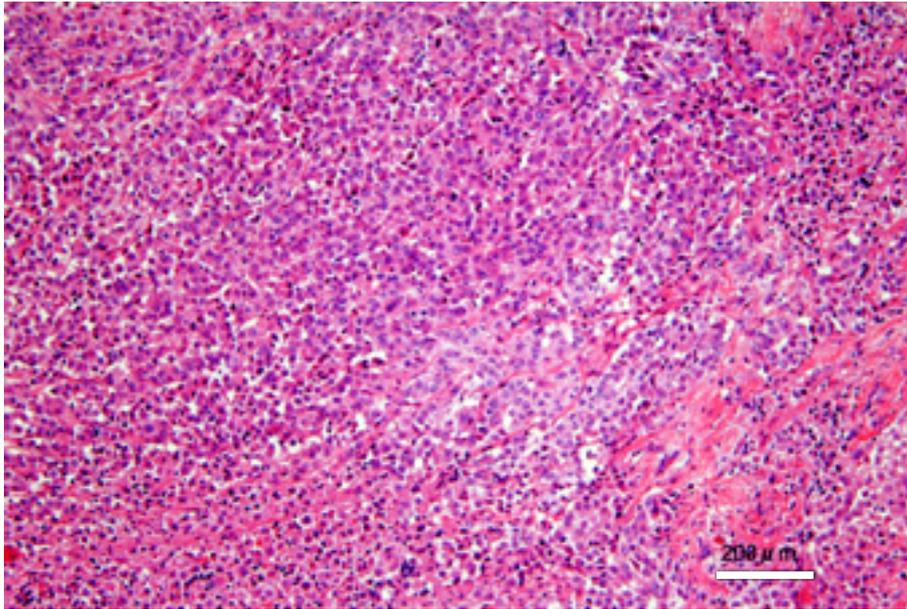


Fig. 3. Keratinization is not seen (hematoxylin and eosin). Bar = 200 μm .

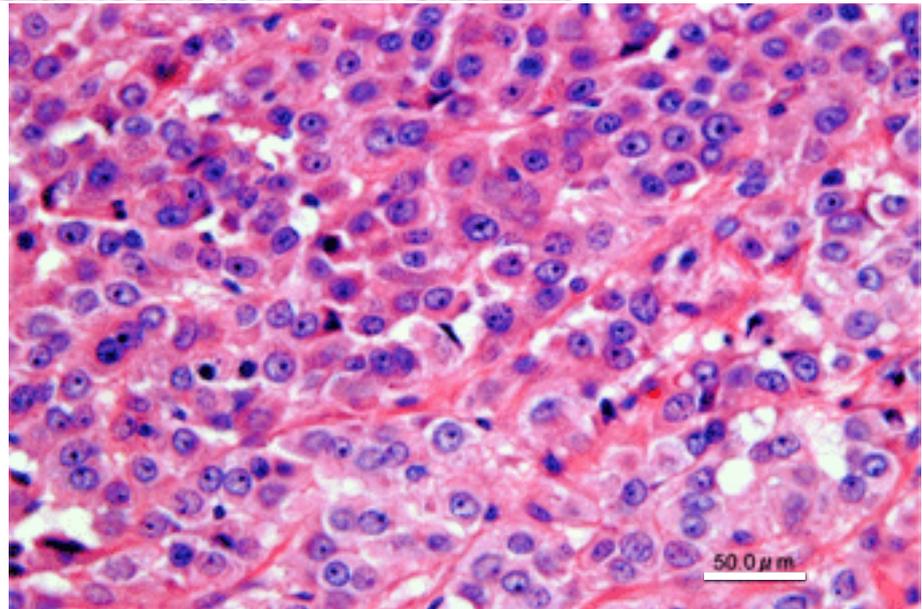


Fig. 4. Tumor cells, arranged in palisades and sheets, show large, atypical nuclei (hematoxylin and eosin). Bar = 50 μm .

ifferentiated carcinoma includes other primary salivary gland neoplasms: adenoid cystic carcinoma, epidermoid carcinoma, malignant melanoma, adenocarcinoma, poorly differentiated squamous cell carcinoma, lymphoma and sarcoma. In our patient, fine-needle aspiration cytologic examination resulted in a provisional diagnosis of adenocarcinoma versus pleomorphic adenocarcinoma. It was reported that high grade mucoepidermoid carcinoma or poorly differentiated adenocarcinoma or squamous cell carcinoma or melanoma could not be ruled out because of cytomorphological overlap (Moore and Bocklage, 1998).

Undifferentiated carcinomas of the submandibular gland occur in adults. Patients have ranged in age from 40 to 96 years, with the peak incidence in the 7th and 8th decades (Ellis and Auclair, 1996). However, 4 of 6 patients in 1 series were under 50 years old (Nagao et al., 1982). Rapid growth of a recently discovered mass is a common clinical presentation. Tumors typically are firm and fixed. Many patients already have cervical lymphadenopathy at the time of diagnosis of the primary salivary gland carcinoma (Ellis and Auclair, 1996). Patients generally are treated with surgical excision, ipsilateral neck dissection

and postoperative radiotherapy, with 50 to 60 Gy delivered over 5 to 6 weeks (Hui et al., 1990).

The prognosis of large-cell undifferentiated carcinoma of salivary glands is poor, with a 10-year survival rate of 0% to 35% reflecting distant metastasis and recurrence. Various subtypes and other histopathologic features of undifferentiated carcinomas have had little prognostic importance (Hui et al., 1990), with tumor size being the most important prognostic factor. Neoplasms 40 mm or larger had a particularly poor outcome (Hui et al., 1990). Wang et al. reported 3 factors predicting a poor outcome for these patients: age over 50 years, cervical lymph node metastasis and tumor size over 60 mm. Locoregional control was obtained much more often in patients with smaller primary neoplasms (Wang et al., 2004).

It has not yet been confirmed whether chemotherapy is effectively inhibits loco regional recurrence or distant metastasis. Hatta et al reported that chemotherapy should be administered when tumor diameter exceeds 4 cm is agreeable, because prognosis becomes very poor (Hatta et al., 2003). Chemotherapy has not been administered to our patient, considering that the tumor size did not exceed 4 cm. Aggressive chemotherapy may worsen the patient's performance status. Continuously further investigation is necessary to clarify the effectiveness of adjuvant chemotherapy.

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