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A Case of Metastasis to the Submandibular Gland from Small Cell Lung Carcinoma (SCLC)

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Metastases to the salivary glands from distant neoplasms are unusual. Most reported cases of salivary gland neoplasms involve the parotid gland. Metastatic deposits in the submandibular gland are extremely rare. Herein, we present a case of lung carcinoma with submandibular gland metastasis. The clinical course is described and discussed with reference to the literature.

Key words: submandibular gland, metastasis, lung carcinoma

Introduction

Metastatic spread restricted to major salivary glands is uncommon. Most salivary gland neoplasms involve the parotid gland, followed by the submandibular gland. We have been able to find only 10 examples[1)~6)] in the English and Japanese literature on pulmonary cancers metastases to the submandibular gland.

Small cell lung carcinoma (SCLC) is a common neoplasm that represents 15-20% of all lung cancers[7)]. Patients with SCLC occasionally present with symptoms caused by metastatic disease without pulmonary symptoms. Common sites of metastasis include liver, bone and the central nervous system, and submandibular gland presentation is rare[7)]. We report a case of SCLC diagnosed after recognition of the metastatic lesions.

Case Report

An 82-year-old Japanese man presented in July 12, 2001, with a 6-week history of painless swelling in the left submandibular region, measuring 25×22 mm, and submental lymph node swelling. The patient had a smoking history of 40 cigarettes/day. Family history was unremarkable. Intraoral examination revealed no swelling or redness. Magnetic resonance imaging demonstrated a poorly defined, irregularly expanding mass displaying low intensity in the left submandibular gland, and adenopathy in the submental region of the neck (Fig. 1a), and ^{67}Ga-citrate scintigraphy revealed a hot-spot area in the submandibular region, the other organs showed no abnormality. Chest radiography showed reticulonodular shadows in bilateral lungs (Fig. 1b). We consulted with the respiratory center about his pulmonary lesion. On chest radiography, a reticular lesion was seen and followed, and the left submandibular tumor was treated first because the tumor was increasing in size. The decision was made to thoroughly investigate the chest postoperatively. As the submandibular mass had increased in size, the patient was taken to the operating room for left submandibular gland excision biopsy. Diagnosis was not attempted with fine needle biopsy in this case, as insufficient volume of tissue would have been provided.

Result

Histopathological findings

The left submandibular gland was resected and yielded a specimen measuring 42×35×22 mm, containing a gray-white irregular nodule 25 mm in

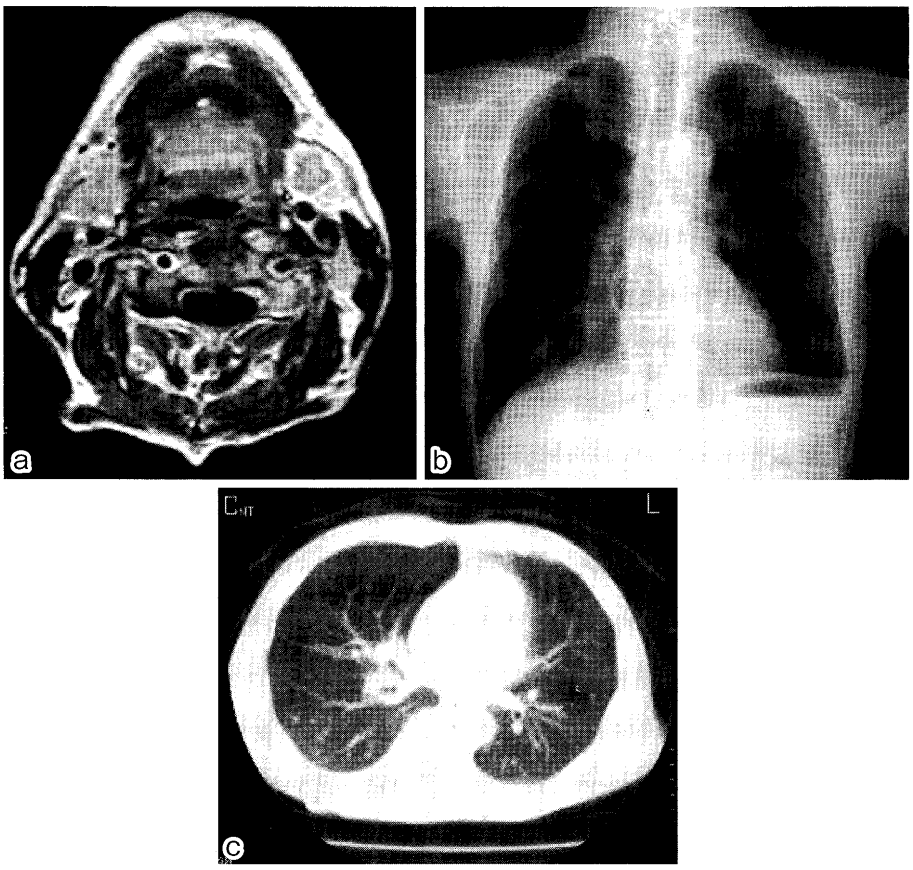

Fig. 1 MRI shows a poorly defined irregularly expanding mass that appeared low in intensity in the left submandibular gland (a). Chest radiography shows reticulonodular shadows in bilateral lungs (b). CT shows a right lower lobe mass in contact with the right main stem bronchus (c).

maximum diameter. The tumor comprised solid nests, broadly infiltrating the submandibular gland. Microscopic examination showed tumor cells arranged in sheets and cords with ovoid nuclei and minimal cytoplasm. Cells had infiltrated adjacent submandibular glandular parenchyma, without an intervening pseudo-capsule. Tumor cells were as large as or slightly larger than lymphocytes. Numerous mitosis and tumor necrosis were present (Fig. 2a, b).

Immunohistochemical findings

The major tumor cells stained positively for epithelial membrane antigen (EMA), CD 56, and neuron-specific enolase (NSE). However, no staining was seen for vimentin, α-smooth muscle actin (α-SMA), S-100 protein (S-100), synaptophysin (Syn) or chromogranin (Chr) A. Electron microscopic examination revealed few neuroendocrine granules in the cytoplasm of cells. Small cell carcinoma (SCC) was diagnosed, with lymphatic metastases in a submental lymph node.

The patient underwent whole body examination. Computed tomography (CT) of the chest showed a right lower lobe mass in contact with the right main stem bronchus (Fig. 1c). CT of the brain and abdomen revealed metastases to the brain, kidney and adrenal gland. We consulted with a chest physician about the pulmonary lesion and possible treatment. Chemotherapy was initiated, but tumor metastases to the brain and spine developed and the patient suffered from confusion and incontinence. He developed acute interstitial pneumonia on September 19 and the patient died.

Autopsy findings

Lung tumor, measuring 40 mm in diameter, was found in the region of the right lower lobe bronchus.

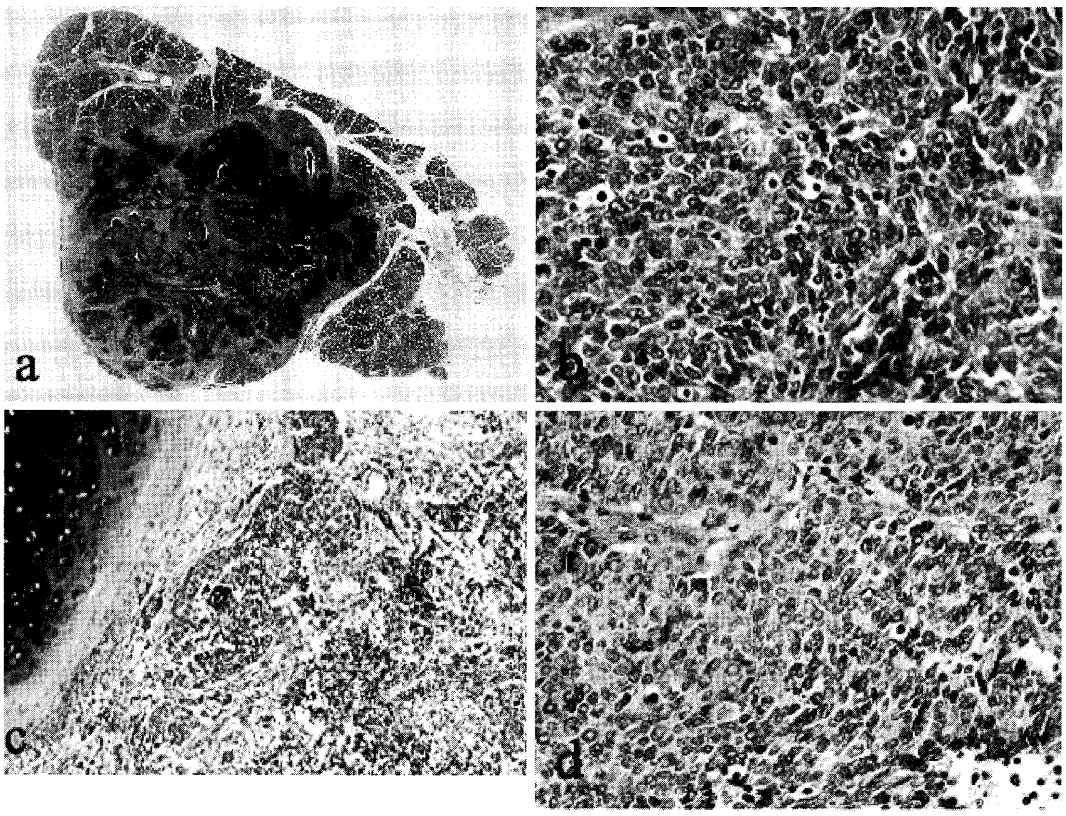

Fig. 2 Photomicrography shows tumor cells arranged in sheets and cords with ovoid nuclei and minimal cytoplasm and cells infiltrating the adjacent submandibular lobule (HE ×2 (a); HE ×200 (b)), showing invasive SCLC of the lung. Tumor cells show features identical to those of submandibular glands (HE ×20 (c); HE ×200 (d)).

The lesion had spread extensively through the lamina propria and invaded the bronchial wall and adjacent lung. Metastases were identified in bilateral hilar lymph nodes, in addition to the kidney, liver, colorectum and adrenal gland. Examination of the brain was not performed, as consent was unable to be obtained from the patient's family.

Microscopically, lung tumor cells had features identical to those of the submandibular glands (Fig. 2c, d). Immunohistochemical examination of lung tumor cells demonstrated that major tumor cells showed positive staining for EMA, CD56 and NSE. However, tumor cells did not stain for vimentin, α-SMA, S-100, Syn or Chr. Electron microscopy revealed few neuroendocrine granules in the cell cytoplasm. Final diagnosis was SCLC.

Discussion

SCLC displays a very aggressive clinical course with frequent widespread metastases. At presentation, approximately 30% of patients have low-stage and 70% have high-stage disease. SCLC is regarded as a systemic disease, as almost all patients display metastases to regional lymph nodes and extrathoracic sites at the time of initial presentation[7].

Up to 5% of SCLC patients have no apparent pulmonary or mediastinal lesions on chest radiography. Any of either have extrapulmonary primary tumors in organs such as the larynx, esophagus, colon, bladder and cervix, or have disseminated metastases but no detectable primary tumor[7].

The case described herein is particularly interesting because submandibular gland metastasis was the initial presentation for lung carcinoma.

Metastatic spread of carcinoma to the major salivary glands is uncommon. According to a study by the Armed Forces Institute of Pathology, the site of primary tumor was known in only 14 patients (19%). In 6 of these 14 patients (43%), primary tumor was found in the head and neck, while tumors in the remaining 8 patients (57%) arose from distant sites[2].

Review of a further 30 cases from another study revealed similar data with an even higher percentage (73.3%) of metastases to the submandibular gland from distant sites versus only 13.3% from the head and neck region (in 13.3% of cases, primary sites were unknown)[2]. The reason for the rarity of metastases to the submandibular gland, as compared to the parotid gland, is unclear, but may be due to a lack of lymphatic vessels within the submandibular gland[8]. SCC most frequently arises in the lung. An extrapulmonary origin is uncommon, and SCC originating in submandibular glands is extremely rare. Comparison between the submandibular tumor and lung carcinoma revealed very similar morphological features in this case. Immunohistochemical and ultrastructural features were also similar. The histological features in this case do not conclusively exclude a primary lesion of the submandibular gland, but are strongly suggestive of an extrasalivary origin. Combined with the clinical features, the characteristics provide compelling evidence of metastasis from primary tumor of the lung.

The differential diagnosis of SCLC includes typical carcinoid tumor, atypical carcinoid tumor, and large cell neuroendocrine carcinoma (LCNEC)[9][10]. In SCLC, mitotic rates are high and necrosis tends to be extensive while in carcinoid tumors the rates are low and necrosis tends to be focal. Unlike SCLC, however, LCNEC is composed of cells larger than 30 μm in diameter, with a moderate nucleocytoplasmic ratio, coarse chromatin, and conspicuous nucleoi[9][10]. Matsuki et al have reported that the neuroendocrine (NE) markers (Syn, Chr, CD56, NSE) are negative in 1 of the 23 cases of the SCLC. On the other hand 78% of cases (18/23) are positive for three or more NE markers[11]. In this case, tumor cells are as large as or slightly larger than lymphocytes. Numerous mitosis and tumor necrosis are present. The demonstaration of positive immunostaining for CD56 and NSE supports the diagnosis of SCLC. Furthermore, electron microscopic examinations reveal few neurosecretory granules in the cell cytoplasm.

Lung tumor was suspected to have arisen in a left submandibular lymph node and invaded the submandibular gland following extracapsular spread, and the submental lymph node also displayed involvement of the lung tumor. Carter and Eggleston stress that metastasis from an occult lung carcinoma should always be considered in the differential diagnosis of SCC in extrapulmonary sites[12]. They note that SCLC may produce extensive metastases while the primary tumor remains small or clinically inapparent[12]. Consequently, in cases of submandibular gland tumor, the rare possibility of localization in the lung should be considered.

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顎下腺転移を認めた肺小細胞癌の1例

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小細胞癌は肺に好発する未分化癌で早期より多臓器へ転移する特徴がある．しかし唾液腺への転移はまれで，なかでも顎下腺への転移はきわめてまれである．今回われわれは肺小細胞癌が顎下腺に転移した症例を経験したので文献的考察を含めて報告する．

患者は82歳男性で，顎下部の腫脹を主訴に2001年7月に来院した．左顎下部に鶏卵大，弾性硬の腫瘤を認め，またオトガイ下に拇指頭大のリンパ節を触知した．Gaシンチでは左顎下部に集積を認めたが，その他異常を認めなかった．頸部MRIではT1強調像にて左顎下腺下極に25×22mm大で類円形，内部不均一，境界不明瞭なlow intensity massを認め，オトガイ下リンパ節の腫脹も認められ，顎下腺悪性腫瘍が疑われたため，左顎下腺腫瘍切除生検術を施行した．腫瘍は類円形で顎下腺下極に癒着しており，割面は充実性で黄白色を呈していた．病理組織学的には顎下腺小細胞癌，オトガイ下リンパ節転移との報告であったため，全身精査を行った．胸部CTにて右肺門部付近に15mmの腫瘤を認めたため東京女子医科大学呼吸器内科を受診したところ原発性肺癌の可能性が示唆された．その他画像診断で腎臓，副腎，脳に転移が認められた．化学療法を予定していたが，脳転移による痙攣，意識レベルの低下が認められ傾眠傾向となったため施行せず，間質性肺炎のための呼吸不全で死亡した．剖検では右肺下葉気管支に原発巣と考えられる腫瘍を認めた．病理組織学的には肺小細胞癌の顎下腺転移と診断し，その他腎臓，肝臓，副腎，小腸に遠隔転移を認めた．

小細胞癌は肺に好発する未分化癌で，腫瘍の進展速度が急速のため，診断時点でリンパ節転移や遠隔転移をきたしていることも多い．唾液腺への転移はまれで，なかでも顎下腺への転移はきわめてまれであるが，顎下腺腫瘍を認める場合には肺癌の転移も念頭に置く必要があると考える．