Journal of Dental Sciences (2017) 12, 413–416

Available online at www.sciencedirect.com

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Case Report

Primary small cell carcinoma with neuroendocrine properties of the mandible: A case report and literature review

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Final revision received 15 January 2012; accepted 16 March 2012
Available online 17 November 2012

KEYWORDS
chemotherapy;
immunohistochemistry;
mandible;
neuroendocrine system;
small cell carcinoma

Abstract Small-cell carcinomas at extrapulmonary primary sites are rare but they have been documented to arise at various locations. We report a case of small-cell carcinoma arising in the mandible, which has so far not been reported in the literature. A 37-year-old male patient underwent partial resection of the left mandible and adjuvant chemotherapy. Immunohistochemistry confirmed the diagnosis of small-cell carcinoma with neuroendocrine properties. The patient has been free of disease for 18 months after receiving treatment and was alive at the time of writing. We recommend surgical resection followed by chemotherapy for managing small-cell carcinomas in the mandibular region.

Introduction

Small-cell carcinomas (SmCCs) are anaplastic, highly malignant carcinomas that are mainly bronchogenic. Extrapulmonary sites account for only 4% of all SmCCs.[1] SmCCs rarely originate in the head and neck region. Survival differs between locations. The median survival time is 8 months for SmCCs of the renal pelvis,[2] whereas the 5-year survival rate for primary submandibular gland SmCCs

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http://dx.doi.org/10.1016/j.jds.2012.03.020

is 40%.[3] These malignant tumors are composed of undifferentiated small cells and exhibit neuroendocrine differentiation by immunohistochemistry. The purpose of this report was to present a single, rare case of SmCC that originated from the mandible with neuroendocrine properties, based on immunohistochemistry, and describe a viable treatment option.

Case presentation

A 37-year-old man was admitted with a complaint of pain in the left lower posterior teeth for 2 months and numbness in the left lower lip for 20 days. The patient denied a history of tobacco smoking, and his medical history was noncontributory. His chest X-ray showed no signs of space-occupying lesions in the lungs and no findings suggestive of pulmonary neoplasia. Clinical examination showed a tender, unmovable swelling on the mandible, numbness of the skin of the left lower lip, and no palpable lymph nodes in the bilateral submandibular region. Intraoral examination showed a 2 cm × 2 cm tender mass on the buccal side of the left molar region. The teeth involved were firm with no dislocation, and the overlying mucosa was normal.

A panoramic radiograph revealed that an ill-defined radiolucency of about 1 cm × 1.5 cm in diameter was involved in the root apex of the left lower first molar, and the lesion exhibited invasive characteristics of root resorption and periodontal ligament space widening (Fig. 1A). A computed tomography scan showed bone resorption of the buccal mandible body from D3 to D6 (Fig. 1B).

Laboratory data were within normal ranges. Tumor markers including α-fetoprotein, carcinoembryonic antigen, total prostate-specific antigen, carbohydrate antigen 19-9, and carbohydrate antigen 125 were tested.

The examination results suggested a primary malignancy of the mandible (cT1cN0cM0). During the operation, a frozen biopsy was performed, which demonstrated multiple small round cells exhibiting atypia consistent with a malignant neoplasm. Then, partial resection of the left mandible was performed. The continuity defect of the mandible from the midline to the third molar was reconstructed using a vascularized free fibular flap. The healing process was uneventful. The patient received adjuvant chemotherapy of six courses using cisplatin (40 mg/m^2) and etoposide (130 mg/m^2). Regular and aggressive follow-up every 1–3 months was carried out. No evidence of local recurrence or metastasis was observed 18 months after treatment (Fig. 1C and D). After surgery, the chewing of food and speech intelligibility were partially affected, whereas tongue mobility, swallowing, and breathing were normal.

On gross observation, the excised biopsy sample measured 3 cm × 2.5 cm, was hard, and appeared grayish-white. The pathological characteristics of the surgical sample revealed many scattered small foci of tumor cells with a cicatrized fibrous stroma in the musculoadipose tissue (Fig. 2). Therefore, an undifferentiated small-cell malignant tumor of the mandible was diagnosed. Assessment of the surgical margins showed that all margins of the tumor were negative. No tumor was found in any of the resected regional lymph nodes. The pathological stage was pT2N0M0 (margin negative) according to the pathological examination.

Subsequent immunohistochemistry demonstrated positive staining for cytokeratins AE1/AE3, CD56, synaptophysin, chromogranin A, and glial fibrillary acidic protein (Fig. 3A–C), and negative staining for myogenic differentiation 1, epithelial membrane antigen, S-100 protein, CD3, CD20, CD43, CD79a, CD99, leukocyte common antigen (CD45), B-cell lymphoma 2 (BcL-2), human melanin black

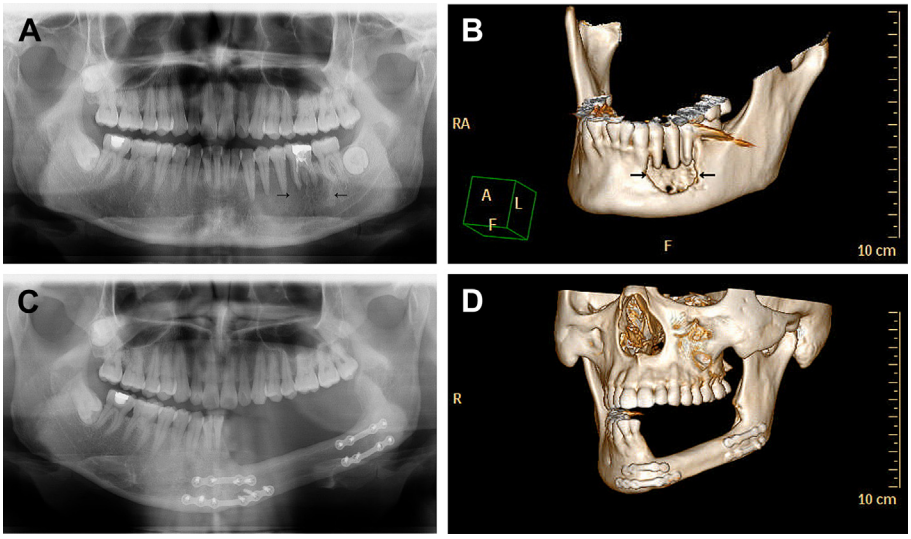

Figure 1 (A) Panoramic radiograph showing ill-defined radiolucency of the left mandible involving the apex of D6, root resorption, and periodontal ligament space widening. (B) Preoperative computed tomography scan showing a bone defect from D3 to D6. (C) Panoramic radiograph 18 months after surgery showing no absorption on either end of the fibular graft and good healing. (D) Computed tomography scan 18 months after the patient underwent surgery and adjuvant chemotherapy.

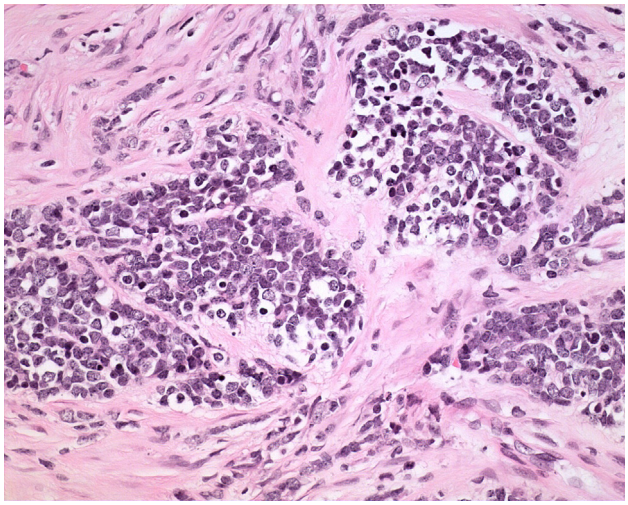

Figure 2 Scattered small foci of tumor cells with a cicatrized fibrous stroma in the musculoadipose tissue (hematoxylin and eosin, 40×).

(HMB)-45, melan-A, myeloperoxidase, and thyroid transcription factor (TTF)-1 immunostaining (Fig. 4).

Discussion

SmCCs are anaplastic, highly malignant, and usually bronchogenic carcinomas that account for 14% of bronchogenic carcinomas.[4] Extrapulmonary sites account for only 4% of all SmCCs.[1] SmCCs rarely originate in the head and neck region, and the larynx, pharynx, nasal cavity, paranasal sinus, cervical esophagus, proximal trachea, and oral cavity are locations in the head and neck from which an SmCC may arise.[3] To the best of our knowledge, there is no report in the literature of an SmCC primarily localized in the mandible. There is a low incidence of jaw metastasis, which is thought to be because the jaw has less cancellous bone than other bones.[5] The premolar–molar region is the most common site of localization, due to a predominance of red bone marrow and retardation of the circulation in this area.[6] Although the occurrence of an SmCC in the jaw has not been reported, a primary SmCC of the mandible was first considered in our case, but the possibility that the current tumor was a metastatic SmCC arising from the lung was excluded because no space-occupying lesion was found on chest X-ray examination. However, the possibility that this might represent a metastatic lesion from a small occult primary source of <2 cm in size was excluded only after immunohistochemical analysis.

Immunohistochemistry is a very important and the most significant tool in differentiating between small round cell tumors with different histogenetic origins. Positive staining for cytokeratins (AE1/AE3) confirmed that the tumor was epithelial in nature. Chromogranins are metrical proteins that are associated with neurosecretory granules and are absolutely specific for neuroendocrine differentiation.[7] Synaptophysin is associated with presynaptic nerve cell vesicles. Neuron-specific enolase is used as a screening agent for its low specificity and sensitivity for neuroendocrine tumors. Other markers expressed in neuroendocrine tumors of the head and neck are anticytokarin (CAM 5.2), epithelial membrane antigen, carcinoembryonic antigen, calcitonin, and S-100 protein. Negative staining with leukocyte common antigen and HMB-45 can exclude a diagnosis of malignant lymphoma and melanoma. The

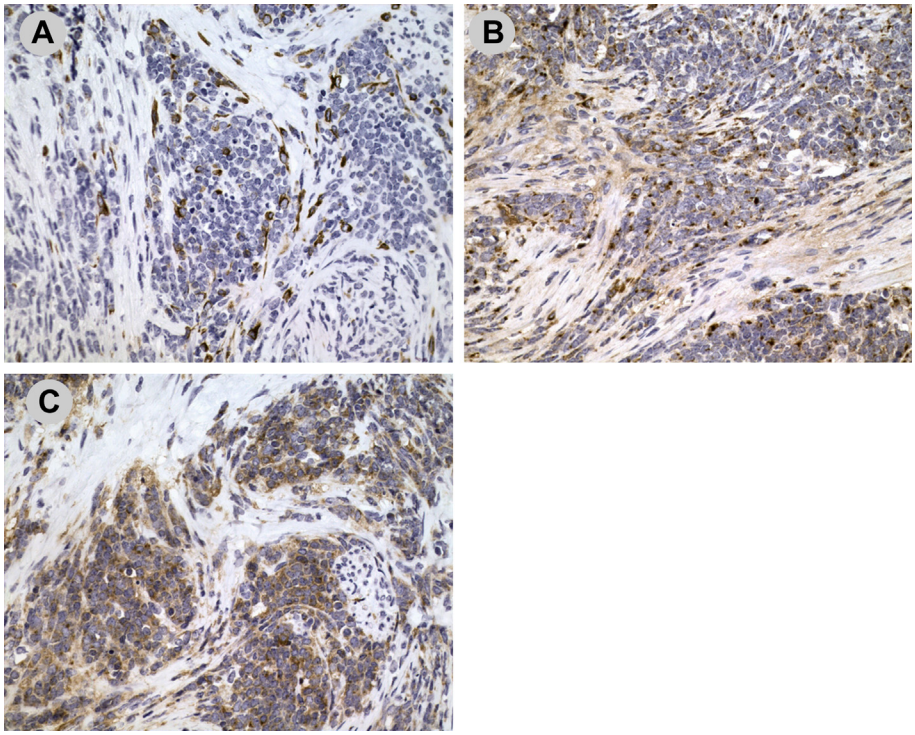

Figure 3 Immunohistochemistry staining positive for (A) glial fibrillary acidic protein, (B) chromogranin A, and (C) synaptophysin.

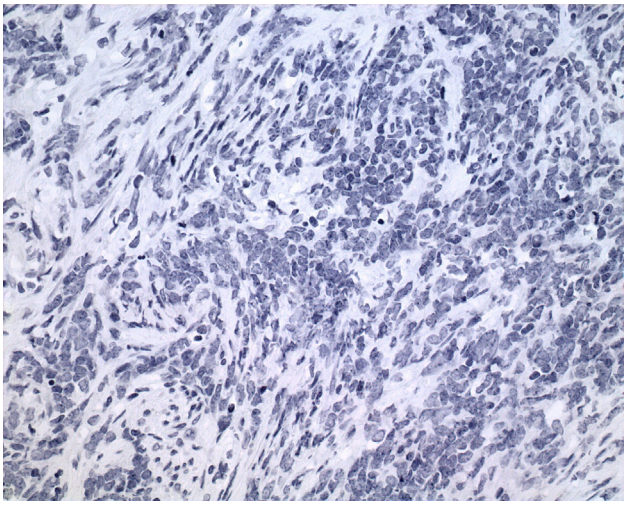

Figure 4 Negative immunohistochemical staining for thyroid transcription factor-1.

pattern of immunostaining in this case led to a diagnosis of SmCC with neuroendocrine properties. TTF-1 is normally expressed only in thyroid and lung cells. For SmCCs of various extrapulmonary sites, TTF-1 staining is usually positive (50%), whereas for small-cell lung carcinoma, TTF-1 staining is 90% positive. The negative TTF-1 staining in this case essentially ruled out metastatic lung cancer.

Small-cell tumors of the bone are a heterogeneous group of neoplasms that share overlapping clinical, radiological, morphological, and immunohistochemical features. Small-cell osteosarcomas resemble Ewing sarcomas or conventional osteosarcomas radiologically. The presence of mineralized matrix in imaging studies supports a diagnosis of an osteosarcoma and is helpful in differentiating other small-cell tumors of the bone. In our case, this was ruled out by the absence of osteoids. Chondroid foci are stained for S100 protein, and primitive mesenchymal cells are positive for CD99. Therefore, both S100 and CD99 being negative ruled out a mesenchymal chondrosarcoma. Neuroblastomas can present as bone metastases and can be distinguished from other primary round-cell tumors of the bone by immunohistochemical positivity for neuron-specific enolase, synaptophysin, and chromogranin, and the absence of staining for CD99, lymphoid markers, desmin, myogenin, and myogenic differentiation 1. However, in our case, that could not be ruled out.[8]

The prognosis of patients with a primary SmCC of the head and neck is generally poor. Proportions of patients surviving to 1 and 2 years were 63% and 26%.[9] Overall, primary SmCCs of the salivary glands have a better prognosis than SmCCs found in other areas of the head and neck, or lungs.[10] The 2- and 5-year survival rates were reported to be 70% and 46%, and 1- and 5-year survival rates for submandibular glands were 71% and 40%, respectively.[4]

The paucity of SmCCs of the head and neck has led to a lack of studies drawing major conclusions or providing treatment recommendations. The combined modality therapy of surgery, chemotherapy, and radiotherapy is used for extrapulmonary SmCCs.[10] Radical excision and adjuvant chemotherapy using cisplatin (40 mg/body mass index) and etoposide (130 mg/body mass index)[11] seem to be good options for SmCCs in the head and neck area. Treatments fail because of regional recurrence and distant metastasis; however, local recurrence is not frequently reported with this disease.

Here, we reported a case of an extremely rare SmCC occurring in the mandible. It had a better prognosis than tumors in other extrapulmonary sites. Moreover, we consider that surgical resection followed by chemotherapy should be recommended for managing SmCCs in the mandibular region.

Acknowledgments

The authors would like to thank Prof. Henning Schliephake (Department of Oral and Maxillofacial Surgery, Georg August University, Goettingen, Germany) for valuable advice on this paper.

References

1. Howard S, O'Regan K, Jagannathan J, Krajewski K, Giardino A, Ramaiya N. Extrapulmonary small cell carcinoma: a pictorial review. *Am J Roentgenol* 2011;197:W392—8.
2. Fukushima H, Koga F, Tatokoro M, et al. Successful treatment with multidisciplinary therapy including low-dose chemo-radiotherapy against metastatic recurrences of small cell carcinoma of the renal pelvis: a case report. *Nihon Hinyokika Gakkai Zasshi* 2011;102:638—43.
3. Gnepp DR, Wick MR. Small cell carcinoma of the major salivary glands. An immunohistochemical study. *Cancer* 1990;66:185—92.
4. Travis WD. Update on small cell carcinoma and its differentiation from squamous cell carcinoma and other non-small cell carcinomas. *Mod Pathol* 2012;25:18—30.
5. Stockdale CR. Metastatic carcinoma of the jaws secondary to primary carcinoma of the breast. *Oral Surg Oral Med Oral Pathol* 1959;12:1095—101.
6. van der Kwast WA, van der Waal I. Jaw metastases. *Oral Surg Oral Med Oral Pathol* 1974;37:850—7.
7. Wick MR. Immunohistology of neuroendocrine and neuroectodermal tumors. *Semin Diagn Pathol* 2000;17:194—203.
8. Hameed M. Small round cell tumors of bone. *Arch Pathol Lab Med* 2007;131:192—204.
9. Hatoum GF, Patton B, Takita C, et al. Small cell carcinoma of the head and neck: the University of Miami experience. *Int J Radiat Oncol Biol Phys* 2009;74:477—81.
10. Renner G. Small cell carcinoma of the head and neck: a review. *Semin Oncol* 2007;34:3—14.
11. Lin YC, Wu HP, Tzeng JE. Small-cell undifferentiated carcinoma of the submandibular gland: an extremely rare extrapulmonary site. *Am J Otolaryngol* 2005;26:60—3.