Case Report

Simultaneous primary mucosal malignant melanoma of the oral cavity and squamous cell carcinoma of scalp: a case report and literature review

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Abstract: We report one case of combining primary malignant melanoma (MM) in gingival mucosa and scalp squamous cell carcinoma (SCC) and review the literature. The patient was a 31-year-old man who had a 120-day history of one nodule in the left gingiva with three gradually enlarging masses in the left lower jaw and a mass in the scalp of the right occiput. Magnetic Resonance Imaging (MRI) revealed a well-defined borderline nodule in the left gingiva and a mass in the scalp of the right occiput with enlargement of lymph nodes in bilateral lower jaw and cervix. The diagnosis was primary MM in gingival and primary cutaneous SCC with metastasized lesions in submandibular and cervical lymph nodes. The patient adopted combined treatment consisting of operations, chemotherapy and cellular therapy. He has been alive for 29 months from the date of diagnosis. Simultaneous occurrence of non-cutaneous primary MM and SCC is extremely rare, especially simultaneous primary oral mucosal MM and scalp SCC in our case. The biological behavior of such simultaneous double tumors is still uncertain and needed further investigation.

Keywords: Oral mucosal malignant melanoma, cutaneous squamous cell carcinoma, simultaneous double tumors

Introduction

Squamous cell carcinoma (SCC) and malignant melanoma (MM) are very prevalent and rapidly increasing malignancies [1-3]. Two or more kinds of tumors with different biological behaviors and histopathologic entities could be seen in one patient [4]. Previous studies showed the simultaneity of primary non-cutaneous SCC and MM is extremely rare [5-8]. Herein, we present one case of combining primary malignant melanoma (MM) in gingival mucosa and scalp squamous cell carcinoma (SCC) and reviewed the literature.

Materials and methods

Patient selection

Ninety-three cases of malignant melanoma (MM) and 8406 cases of squamous cell carcinomas (SCC) were collected from the Department of Pathology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, between January 2012 and July 2016. All cases were histologically and immunophenotypically reviewed, and the diagnosis was based on the World Health Organization (WHO) classification of Pathology and Genetics of Head and Neck Tumors [2], Pathology and Genetics of Skin Tumors [1] and tumors of the Digestive System [3]. In total, one case of primary oral malignant melanoma with primary cutaneous squamous cell carcinoma was identified. The clinical and laboratory data of this patient was collected and tumor staging evaluated according to the TNM classification [1-3].

Hematoxylin and eosin (HE) and immunohistochemical staining

Four micrometer-thick sections from formalin fixed paraffin embedded blocks were cut for routine hematoxylin and eosin staining. The
EnVision method was used for immunostaining with diaminobenzidine (DAB) as a substrate. A broad panel of antibodies included: Vimentin (V9), Melan-A (A103), HMB45 (HMB45), S-100 Protein (4C4.9), cytokeratin (CK; AE1/AE3), CK5&6 (D5/16B4), CK8&18 (5D3), Desmin (D33), MyoD1 (5.8A), CD34 (QBEnd/10) and Ki-67 Antigen (MIB-1). All antibodies were purchased in Beijing Zhongshan Biotechnology Co (Beijing; China). The slides were treated by pressure-cooking in citric acid buffer (10 mM, Ph 7.4) for 3 min before staining for Vimentin, Melan-A, HMB45, S-100, CK, CK8&18 and CD34, and in ethylenediaminetetraacetic acid (EDTA; 1 mM, Ph 9.0) for 8 min before staining for CK5&6, MyoD1 and Ki-67. HE and immunohistochemical staining was evaluated by two independent observers who were blinded to clinical data. All of the experiments were repeated three times. Differences were discussed to reach consensus.

A 31-year-old man was referred to Sun Yat-sen Memorial Hospital in October 2014, with a 120-day history of one nodule in the left gingiva with three gradually enlarging masses in the left lower jaw and a mass in the scalp of the right occiput. The mass in gum had a well-defined borderline with ulceration. His physical examination on admission was unremarkable and revealed no evidence of any pigmented lesions on his skin. The patient had no history of alcohol and tobacco abuse. Magnetic Resonance Imaging (MRI) revealed a well-defined borderline nodule in the left gingiva and a mass in the scalp of the right occiput with enlargement of lymph nodes in bilateral lower jaw and cervix (Figure 1). Chest radiograph showed no evidence of metastasis in the lung and the liver scan was negative. The patient underwent an extended resection for the mass in the left gingiva and a partly resection for the left jawbone with a left neck dissection.

**Figure 1.** MRI imaging features of oral primary malignant melanoma with cutaneous primary squamous cell carcinoma in this series. L, left: A-D. MRI imaging, A. Primary malignant melanoma of gingiva (black arrow). B. Metastasized lesion of malignant melanoma in lymph node (white arrow). C. Primary squamous cell carcinoma of scalp (white arrow). D. Metastasized lesion of squamous cell carcinoma in lymph node (white arrow).

**Review of literature and statistical analysis**

Articles from 1953 to 2016 that contain the keywords “squamous cell carcinoma” and “malignant melanoma” in the PubMed and MEDLINE databases were reviewed. All statistical analyses were performed using the SPSS WIN program package 13.0 (SPSS, Inc, Chicago, IL, USA). Survival time was measured from primary diagnosis until their censoring date. Survival analysis was carried out using the log-rank test in association with Kaplan-Meier analysis. Differences were statistically significant when *P*-value < 0.05.

**Ethical approval**

Each institution obtained approval to participate in the study as required by the local district research ethics committee. Informed consent was obtained from each patient and/or his or her legal guardian.

**Results**

**Clinical features of the patient**
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Diagnosis was primary malignant melanoma (MM) in gingival. Metastasized lesions of MM were found in the left anterior deep cervical and submandibular lymph nodes, respectively. The TNM stage was T4bN2bM0 (IIIC). A month later, the patient was managed with CVD (cisplatin, DDP; vindesine sulfate, VDS; dacarbazine, DTIC) chemotherapy (cisplatin 30 mg/m² on days 1-3, vindesine 2.5 mg/m² on day 1 and dacarbazine 250 mg/m² on days 1-3). After one course of chemotherapy, a resection for the mass in the scalp was taken and the diagnosis was primary cutaneous squamous cell carcinoma (SCC). The day after the operation, cellular therapy (dendritic cells, DC; cytokine induced killer, CIK) at the amount of 2.5×10¹⁰) was given. A month later, the patient came back for the second course of CVD chemotherapy and cellular therapy (at the amount of 1.5×10¹⁰). One and a half months later, a gradually enlarg-

**Figure 2.** Pathological characteristics of oral primary malignant melanoma with cutaneous primary squamous cell carcinoma in this series. A-D. Primary malignant melanoma. A. Histopathology of malignant melanoma (HE, original magnificent ×100). B. Tumor cells positive for Vimentin (EnVision method, original magnificent ×100). C. Tumor cells positive for HMB45 (EnVision method, original magnificent ×100). D. Tumor cells negative for CK5/6 (EnVision method, original magnificent ×100). E-I. Primary squamous cell carcinoma. E and F. Histopathology of squamous cell carcinoma (HE, original magnificent ×40). G. Tumor cells positive for CK5/6 (EnVision method, original magnificent ×100). H. Tumor cells negative for Vimentin (EnVision method, original magnificent ×100). I. Tumor cells negative for HMB45 (EnVision method, original magnificent ×100).
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ing mass was found in the right of cervix. The patient was managed with a right neck dissection and the third course of cellular therapy (at the amount of $1.5 \times 10^{10}$). Metastasized lesions of SCC were found in one lymph node of the right posterior cervix and one in the right submaxillary, respectively. However, a recurrent nodule was found in the scalp of the right occiput. The patient underwent the second resection for the scalp mass and was diagnosed recurrent SCC. Then, the fourth and fifth course of cellular therapy (at the amount of $1.0 \times 10^{10}$) was performed. However, nodules were found in the scalp of the right occiput and the right of cervix after one month. Then, a nodule excision of scalp and cervix was conducted and diagnosed as recurrent and metastasized SCC. The patient was discharged in June 2015.

**Pathological features of the patient**

Based on partial resection of the left mandible, radical left cervical lymph node dissection and scalp tumor resection, this case was diagnosed as primary MM in gingiva and cutaneous primary SCC. As for MM, grossly, there was a white or tan, solid mass on the cut surface, measuring approximately $1.5 \times 1.5 \times 1$ cm in the gum, which infiltrated epidermis, striated muscle and mandibular. Histopathologically, a spindle cell proliferation in the lamina propria with a solid, sheet and groove-like pattern of growth, which marked cytologic atypia, nuclear grooves, folds, large eosinophilic nucleoli and abundant mitotic figures, some of them atypical (Figure 2A). Melanin pigmentation was found somewhere. Immunohistochemically, the atypical melanocytes were reactive for vimentin (Figure 2B), Melan-A and HMB-45 (Figure 2C), while negative for S-100, CK, CK5/6 (Figure 2D), CK8/18, desmin, MyoD1 and CD34. Reactive expression of Ki-67 which is an accurate marker of the proliferative index of cells was 50%. Metastasized lesions of MM were found in one lymph node in the left of superior cervix and eight lymph nodes in the left of submaxillary, respectively. Their physical examination on admission was unremarkable and revealed no evidence of any pigmented lesions on their skin. In the study group, the combination of mucosal MM and mucosal SCC that occurred separately but simultaneously in the same organ was diagnosed in three cases, including 2 in the oral cavity [5-6] and one in the esophagus [8].

The first oral case had a chronic, draining oroantral fistula in the right posterior maxillary mucobuccal fold that had been present for 13 years, a 2 cm lesion of MM in the right buccal mucosa and multiple plaques of SCC throughout the floor of his mouth extending to the right anterior tonsillar pillar, and a large, white exophytic lesion was attached to the uvula [5]. The second oral case was found a gradually enlarging dark-brown and pigmented nodule measuring approximately $3.5 \times 4.3$ cm, some separate dark, pigmented spots on the hard palate, maxillary gingival, and the left side of the buccal mucosa and an ulcerative lesion measuring 1.2 cm in diameter. Incisional biopsies of both the dark-brown tumor and ulcerative lesion...
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Table 1. Summary of simultaneous primary squamous cell carcinoma and mucosal malignant melanoma

<table>
<thead>
<tr>
<th>NO.</th>
<th>Author</th>
<th>Age (years)/Gender</th>
<th>Race</th>
<th>History of alcohol and tobacco abuse</th>
<th>Mucosal MM</th>
<th>SCC</th>
<th>Therapy</th>
<th>Relationship between MM and SCC</th>
<th>Follow-up (months and status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kippax JB [5]</td>
<td>50, male</td>
<td>Caucasian-American</td>
<td>Tobacco abuse (positive) alcohol abuse (positive)</td>
<td>The right buccal mucosa</td>
<td>3.5 mm</td>
<td>IIB</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>2</td>
<td>Nakahara H [6]</td>
<td>72, female</td>
<td>Asian-Japanese</td>
<td>Tobacco abuse (NC) alcohol abuse (NC)</td>
<td>Oral</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>3</td>
<td>Sirikanjanapong S [7]</td>
<td>53, male</td>
<td>NC</td>
<td>Tobacco abuse (positive) alcohol abuse (NC)</td>
<td>Larynx</td>
<td>2.8 mm</td>
<td>IIB</td>
<td>Larynx</td>
<td>NC</td>
</tr>
<tr>
<td>4</td>
<td>Hikage M [8]</td>
<td>61, male</td>
<td>Asian-Japanese</td>
<td>Tobacco abuse (NC) alcohol abuse (NC)</td>
<td>The upper thoracic esophagus at 22 cm from the incisors</td>
<td>NC</td>
<td>O</td>
<td>3 cm×1.3 cm</td>
<td>Thoracoscopic subtotal esophagectomy, lymphadenectomy</td>
</tr>
<tr>
<td>5</td>
<td>This report</td>
<td>31, male</td>
<td>Asian-Chinese</td>
<td>Tobacco abuse (negative) alcohol abuse (negative)</td>
<td>Oral</td>
<td>10 mm</td>
<td>IIIc</td>
<td>Scalp</td>
<td>2.5 cm×2 cm×1.5 cm</td>
</tr>
</tbody>
</table>

MM, malignant melanoma; SCC, squamous cell carcinoma; NC, not clear; CR, complete remission; PR, partial remission.
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were performed. The histologic diagnosis of the dark-brown nodule was MM and the ulcerative lesion showed SCC. The patient adopted combined treatment consisting of cryosurgery, immunotherapy, and chemotherapy. Initially, interferon-γ at a dose of $3 \times 10^6$ IU per day and intratumoral injection of a streptococcal preparation, OK-432, at a dose of 10 KE per day (total $240 \times 10^6$ IU doses of interferon-γ, 220 KE doses of OK-432) were used. Cryosurgery and intratumoral injection of interferon-β at a dose of $40 \times 10^6$ IU per course were performed alternately (total $120 \times 10^6$ IU doses of interferon-β). Furthermore, chemotherapy consisting of intraarterial infusion of 10 mg cisplatin (CDDP) and 250 mg 5-fluouracil (5-FU) and of intramuscular injections of 5 mg peplomycin (PEP) per day (total 200 mg CDDP, 5,000 mg 5-FU, and 60 mg PEP) was performed [6].

The case of esophagus was revealed several flat and black pigmented mucosal lesions (2 cm in diameter) in the upper thoracic esophagus at 22 cm from the incisors which was histologically diagnosed as MM. At the same time, a slightly pitted ulcerous lesion (2 cm in diameter) was detected in the abdominal esophagus at 43 cm from the incisors, which was histologically diagnosed as SCC [8].

The case of larynx is the first report recording the combination of mucosal MM and mucosal SCC that not only occurred simultaneously but also admixed consistently with each other, which is called a collision tumor, representing the coexistence of two morphologically distinct tumors [7]. The patient underwent the total laryngectomy and was found a 2.5 cm ulcerated, black, nodular area located on the left laryngeal mucosa, extending from the false vocal cord to the true vocal cord. Microscopic examination revealed in situ and invasive SCC admixed with MM.

To our knowledge, the case of this study is the first case that the combination of mucosal MM and cutaneous SCC occurred separately and simultaneously in different organs.

The patient adopted combined treatment consisting of operations, chemotherapy and cellular therapy. The patient has been alive for 29 months from the date of diagnosis.

21 articles about the combination and simultaneity of cutaneous MM and cutaneous SCC were reviewed [9-30]. These patients were 22 men and seven women, ranging in age from 22 to 72 years at the time of presentation. Most patients were Caucasian. 27 were alive and three died, and the mean time of follow-up was 30.8 months (range, 0.5 to 167 months).

Overall survival time of combination and simultaneity of MM and SCC for one-year, three-year, and five-year were 94.1%, 91.2%, and 91.2%, respectively. Divided into two groups, one group contains cases combining and simultaneous cutaneous MM and cutaneous SCC and the other contains cases combining and simultaneous non-cutaneous MM and SCC. 1-year, 3-year, 5-year overall survival rate of the former group were 93.3.0%, 90.0%, 90.0%, respectively. The survival time between the two groups has no significant difference (Figure 3, $P = 0.486$).

Discussion

Oral squamous cell carcinoma (OSCC) is the most frequent of head and neck malignancies [58]. Although malignant melanoma (MM) is a common cutaneous lesion [62], mucosal melanoma is infrequent [63]. In all of the previously
reported cases, it is common that these two tumors occur simultaneously in skin [9-61]. However, non-cutaneous MM combined with SCC is very rare [5-8]. According to what we searched in English literatures, the combination of non-cutaneous MM and SCC occurred only in 5 cases (including our case), which has a higher incidence in middle aged people. It may be more common in men. These kind of double tumors appear more often separately and simultaneously in the same organ. The case of this study is the first case that the combination of mucosal MM and cutaneous SCC occurred separately and simultaneously, but in different organs.

In most of the cases, mucosal MM is originated from melanocytes in the basal/deeper layers of the epithelium [8]. History of tobacco and alcohol abuse, sunlight, radiation, burning of skin, immunodepression, immunodeficiency and some cancerogenic material like hydrocarbons or arsenic, were the most important factors in the pathogenesis of both MM and SCC [10-12, 16, 30-32, 35, 36, 39, 40, 46-51, 53, 55, 56, 61-64]. Another major cause of their simultaneous or successive appearance in one person is the abnormal expression of signaling molecules during cell proliferation and cell differentiation, such as the expression of p53, cyclinD1, Bcl-2 and proliferating cell nuclear antigen [65, 66]. In the report of Sirikanjanapong S et al [7], it was suggested that both laryngeal mucosal MM and invasive laryngeal mucosal SCC had an overexpression of IL-17A and CD70, eliciting a strong immune response against the tumor resulting in a favorable prognosis. Ile105Val polymorphism of the GSTP1 gene may have genetic contribution to the development of MM [67]. To sum up, genes’ abnormality involved in the mechanisms may play a significant role in progression and prognosis of such malignant tumors.

Like laryngeal SCC, the mainstay treatment for primary mucosal melanoma in the head and neck region is radical surgery with or without adjuvant therapy including radiation and chemotherapy [6]. Generally, radical surgery is the preferred treatment for a localized primary malignant tumor in the oral cavity. However, the second oral case, radical surgery was considered to be impossible because of the extensive involvement by the tumor [6]. In dealing with neoplasms in this region, anatomic considerations often make surgery difficult or impossible. Furthermore, Immunotherapy was incorporated into the treatment of the malignant melanoma, although the patient’s immune response could significantly alter the clinical course of the neoplasm, for which many attempts to therapeutically modulate immune response would be conducted [68-70]. CD24 may be used as a new drug target for malignant melanoma [71].

The depth of invasion of MM and the diameter and infiltrated extension of primary lesion and metastasis of lymph nodes of SCC are the most important prognostic factors [72, 73]. It is generally agreed that the prognosis of oral malignant melanoma remains quite poor when compared with cutaneous melanoma [6]. Many reports showed that simultaneous evaluation of tumor thickness and stage of invasion was of greater value in assessing prognosis of MM than either method alone [72, 73]. The pattern of tumor invasion was more significant than positive surgical margin in predicting local recurrence and overall survival in patients with oral SCC [73]. Therefore, it may be highly possible that the prognosis of combining MM and SCC have an association with the stages of MM and SCC, surgical margin and treatments.

The biological behavior of such unique cases is still uncertain. Thus, future identification of more of such cases and longer follow-up evaluations is still needed to define their biological behaviors.

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Disclosure of conflict of interest

None.

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