Abstract: This report discusses a case of a 75-year-old female patient with metachronous multicentric carcinomas in the oral cavity at 4 different sites. In this patient, there were no generally associated characteristics, such as drinking alcohol, chewing betel quid or smoking cigarettes. However, her elder sister died due to oral carcinoma. Although well-known risk factors for oral carcinoma were not detected, a previous family history was found. These findings suggest the potential for an unknown genetic anomaly associated with oral carcinoma. This is the first report to describe a female patient with oral multicentric carcinoma arising from four different sites.

Keywords: heritable, metachronous, oral multicentric carcinoma

Introduction

Due to an increase in average life expectancy and improvements in cancer therapy, the incidence of oral multicentric carcinomas is increasing. Furthermore, it is known that malignant tumors can independently develop in individuals. In contrast, multicentric carcinoma refers to multiple malignant tumors that have identical histologies that can occur at either the same or at different times. In addition, multiple carcinoma is defined as the occurrence of multiple malignant tumors that exhibit different histological characteristics [1, 2], [Oh JL., Multifocal or multicentric breast cancer: understanding its impact on management and treatment outcomes. Methods of Cancer Diagnosis, Therapy and Prognosis., vol 1, 583-587, Springer, Dordrecht., 2008.].

Recently, developments in cancer diagnosis and treatment have extended the lifespan of individuals who develop these pathologies. However, treating second primary cancer (2nd PC), third primary cancer (3rd PC) and/or fourth primary cancer (4th PC) in the head and neck regions remains difficult.

In the currently reported case, a first primary cancer (1st PC) in the form of a mandibular gingiva carcinoma, which was followed by a 2nd PC in the form of a lip carcinoma, 3rd PC as a soft palate carcinoma, and a 4th PC as a tongue carcinoma were encountered. This is the first report to describe a case of a female patient with oral multicentric carcinomas that arose from 4 different sites.

Case report

In August 2010, a 75-year-old female patient who previously underwent odontectomy that was followed by a subsequent lack of recovery, visited Nihon University itabashi hospital for further evaluation. The patient’s left mandibular second premolar had been extracted by a dentist due to a diagnosis of severe periodontitis in July 2010. Her past medical history included diabetes mellitus, while her family history included the death of an older sister due to oral carcinoma at 88 years old. Past medical histories confirmed that the patient did not drink alcohol, chew betel quid or smoke cigarettes.

During the initial examination, an ulcer measuring 29 × 15 mm, with spontaneous pain in the left mandibular second premolar gingiva was observed (Fig. 1a). Incisional biopsy of the gingival lesion led to a histopathological diagnosis of squamous cell carcinoma (Fig. 1b). Computed tomography (CT) and magnetic resonance imaging (MRI) subsequently detected metastasis in the left cervical lymph nodes and submental lymph nodes. The diagnosis was cT4aN1M0, Stage IVA. In September 2010, tumor excision and selective neck dissection was performed under general anesthesia. After surgery, the patient was followed-up with CT and MRI every 3 months. Postoperatively, TS-1 (100 mg/day) was administered for 22 months. The post-treatment course was uneventful, and at the 22-month follow-up, there were no signs of recurrence or lymph node metastasis identified.

In July 2012, an ulcer measuring 8 × 8 mm was found on her left lower lip (Fig. 2). Incisional biopsy of the left lower lip lesion led to a histopathological diagnosis of squamous cell carcinoma. This tumor was determined to be histologically identical to the 1st PC. Radiotherapy (60 Gy) was performed on the left lower lip after a diagnosis of cT1N0M0, Stage I. Following radiotherapy, the patient underwent follow-up with CT and MRI every 3 months. There were no changes observed during the post-treatment course, and after 52 months of follow-up, there were no signs of recurrence or lymph node metastasis identified.

In February 2017, the patient noticed a strange feeling in her throat and presented to the Department of Otolaryngology. A tumor measuring 8 × 5 mm was found in the soft palate on the left side (Fig. 3). Incisional biopsy of the soft palate lesion led to a histopathological diagnosis of squamous cell carcinoma. This tumor was determined to be histologically identical to the 1st PC. Chemotherapy using docetaxel hydrate (60 mg/m²) and cisplatin (60 mg/m²) was administered at the left soft palate after a diagnosis of cT1N0M0, Stage I tumor. Following the subsequent chemotherapy, the patient underwent follow-up with CT and MRI every 3 months. There were no changes noted during the post-treatment course, and after 17 months of follow-up, there were no signs of recurrence or lymph node metastasis identified.

In September 2018, a tumor measuring 18 × 15 mm was identified on the left side of her tongue with metastasis to cervical lymph nodes on the right side (Fig. 4). Incisional biopsy of the tongue lesion led to a histopathological diagnosis of squamous cell carcinoma, which was determined to have identical characteristics to the previous 1st PC, 2nd PC and 3rd PC. After a diagnosis of cT2N2M0, Stage IVA tumor, in a patient who was adverse to surgery, chemotherapy using nivolumab was administered on the left side of the tongue that exhibited the metastasis to the cervical lymph nodes on the right side. However, 5 months later the nivolumab chemotherapy had to be abandoned due to the development of interstitial pneumonia. Although chemotherapy with TS-1 (80 mg/day) was subsequently started, the patient died after 2 months.

Discussion

Oral multicentric carcinoma is most commonly diagnosed using the criteria described by Warren and Gates [3]. Li et al. [4] additionally applied the following criteria for diagnosing oral multicentric carcinoma: 1) using different regions according to the Union for International Cancer Control (UICC) classification; 2) a distance of ≥ 15 mm between carcinomas is evident on clinical examination; and 3) at surgery, resection margins ≥ 15 mm are achieved. As the frequency of oral multicentric carcinoma has been reported to be 1.6% [5], oral multicentric carcinoma is considered
Table 1  Clinicopathological characteristics of OSCC patients who developed a fourth primary tumor

| Case | Age | Sex | Site       | Stage | Site       | Stage | Site       | Stage | Site       | Stage | Site       | Stage | Reference |
|------|-----|-----|------------|-------|------------|-------|------------|-------|------------|-------|------------|-------|-----------|
| 1    | 45  | Male| Cheek      | pT2N2b| Cheek      | pT2Nx | Lip        | pT1Nx | Gum        | pT4Nx | 5          |
| 2    | 49  | Male| Gum        | pT1N1 | Tongue     | pT3N0 | RM         | pT4Nx | MF         | pT2N2b| 5          |
| 3    | 40  | Male| Tongue     | pT3N0 | Gum        | pT4N0 | Gum        | pT2Nx | Tongue     | pT1N2b| 5          |
| 4    | 35  | Male| Cheek      | pT4N0 | Tongue     | pT2N1 | Tongue     | cT1N0 | Tongue     | cT1N1 | 5          |
| 5    | 55  | Male| Cheek      | pT3N0 | HP         | pT2Nx | Colon      | Dukes'B| Gum        | cT4aN2c| 5          |
| 6    | 35  | Male| Lip        | pT1N1 | Gum        | pT4N0 | Lip        | pT2Nx | Gum        | pT2N2x| 5          |
| 7    | 52  | Male| Cheek      | pT4N0 | Tongue     | pT1N1 | Tongue     | pT1N1 | Gum        | pT2N2x| 5          |
| 8    | 50  | Male| Lip        | pT1N1 | RM         | pT1N0 | Lip        | pT2N0 | SP         | pT1N2x| 5          |
| 9    | 59  | Male| Gum        | pT4N0 | Gum        | pT1N1 | HP         | pT2N0 | TB         | cT4aN0 | 5          |
| 10   | 44  | Male| Cheek      | pT4N0 | Tongue     | cT1N0 | Lip        | cT2N0 | Cheek      | cT1N1 | 5          |
| 11   | 48  | Male| Tongue     | pT2N0 | Gum        | pT4N0 | Lip        | pT3N1 | Gum        | pT4aNx | 5          |
| 12   | 43  | Male| Cheek      | pT2N0 | HP         | pT1N1 | Cheek      | pT2N2x| Gum        | pT4aNx | 5          |
| 13   | 64  | Male| Gum        | pT3N0 | Tongue     | pT2N0 | Cheek      | pT4aN0| TB         | cT4aN0 | 5          |
| 14   | 29  | Male| Tongue     | pT2N2c| RM         | cT1N0 | HP         | cT1N0 | Gum        | pT2N0 | 5          |
| 15   | 45  | Male| RM         | pT2N0 | Lip        | pT2Nx | Inguinal   | pT1N1 | Gum        | pT2N0 | 5          |
| 16   | 50  | Male| Cheek      | pT4N0 | Cheek      | pT2N2b| Tongue     | pT2N0 | Nasal      | cT2N0 | 5          |
| 17   | 47  | Male| Cheek      | pT4N1 | Tongue     | pT4N0 | Gum        | pT1N0 | tonsil     | pT4aN0 | 5          |
| 18   | 66  | Male| Cheek      | pT3N0 | Lip        | pT2N0 | Gum        | pT2Nx | Prostate   | —     | 5          |
| 19   | 49  | Male| Cheek      | pT3N0 | Cheek      | pT1N2b| Gum        | pT1N1 | Tongue     | pT1N1 | 5          |
| 20   | 39  | Male| MF         | pT4N0 | Tongue     | pT1N1 | Lip        | pT1N1 | Gum        | cT2N2cM1| 5          |
| 21   | 56  | Male| RM         | pT1N1 | Tongue     | pT1N2b| Lip        | pT1N0 | TB         | cT4N2c | 5          |
| 22   | 54  | Male| RM         | pT2N0 | Tongue     | pT1N1 | Lip        | pT1N0 | Tongue     | pT1N1 | 5          |
| 23   | 53  | Male| Cheek      | pT2N0 | Cheek      | pT2N0 | Gum        | pT4N0 | Tongue     | pT1N1 | 5          |
| 24   | 42  | Male| Cheek      | pT4N0 | SP         | pT1N0 | TB         | cT2N0 | MF         | cT2N0 | 5          |
| 25   | 49  | Male| Cheek      | pT2N2b| Tongue     | pT1N0 | SP         | pT1N0 | tonsil     | cT2N0 | 5          |
| 26   | 75  | Female| Gum      | cT4aN1M0| Lip        | cT1N0M0| SP         | cT1N0M0| Tongue     | cT2N2cM0| 5          |

HP, hard palate; MF, mouth floor; RM, retromolar trigone; SP, soft palate; TB, tongue base
to be rare. This may be due in part to differences in both the diagnostic criteria and in the follow-up period for oral multicentric carcinoma that is found between hospitals. In addition, the narrow space of the oral cavity can also make it difficult to determine the presence of metastasis and/or recurrence [5]. In the present case of multicentric carcinomas that were located at four different sites in the oral cavity, these were determined to involve metachronous and distant lesions. Under the UICC classification, although the soft palate belongs to the pharyngeal region, it is close to the mandibular gingiva and tongue. As a result, soft palate cancer is considered to represent oral cancer. Moreover, the possibility of the development of metachronous 2nd PC and beyond, that can occur as a result of chemotherapy and/or radiotherapy, is undeniable. The probability of a patient with a history of oral cancer treatment developing 2nd PC has been reported to be 6.3% [6]. The pathogenesis of multicentric cancer is considered to involve the following factors: 1) a lack of apparent causality; 2) field cancerization; 3) endogenous (heritable, constitutional, and hormonal) factors; 4) viral infection; 5) environmental (smoking cigarettes, drinking alcohol, and dietary habits) factors; 6) radiation-related cancer; and 7) tumor immunity factors. Slaughter et al. [7] proposed field cancerization as a term to explain multifocal oral cancers in which clinically occult multifocal preneoplastic foci emerge within the epithelium of an anatomical region exposed to the same carcinogenic factors. The rate of multicentric carcinomas at 4 different sites in the oral cavity appears to be 1.4%. Thus, this case should not be considered to be extremely rare [5]. However, the differences that are seen between past reports for multicentric carcinoma in the oral cavity at 4 different sites and the current case are as follows:

1. Patients in past reports of multicentric carcinomas at 4 different sites in the oral cavity were all male (Table 1), whereas this case was female.
2. The age range of previous patients at identification of the 4th PC was 29-66 years (mean, 49 ± 10.1 years) (Table 1), whereas this case was 75 years old at the 1st PC, which is the oldest patient by a substantial margin.
3. In past patients, the rate of chewing betel quid was 100% (25/25), the rate of drinking alcohol was 72% (18/25), and the rate of smoking cigarettes was 88% (22/25) [5]. In contrast, this case took part in none of these behaviors.

In conclusion, a case with possible unknown genetic anomalies associated with oral carcinoma is reported. This is the first case to be reported that describes a female patient with oral multicentric carcinomas arising from 4 different sites.

Conflict of interest
The authors have no conflict of interest or research funding to declare.

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