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Second primary squamous cell carcinoma in an oral cavity free flap: A case report and review of the literature

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ABSTRACT

Recently, an increasing number of reports have described squamous cell carcinomas arising in free flaps used for maxillofacial reconstruction. Here, we report the case of a patient with second primary carcinoma arising in a free flap, and present a literature review of possible risk factors. A 59-year-old woman was referred to our department complaining of swelling in the lower gingiva in 2012. Her previous history included hypopharyngeal carcinoma for which she had undergone surgery and high-dose radiation therapy. We diagnosed her with osteoradionecrosis, and she underwent mandibular resection and simultaneous reconstruction with an anterolateral thigh flap. In 2016, the patient presented with an exophytic swelling with leucoderma on the free flap. We diagnosed the lesion as a second primary squamous cell carcinoma derived from the free flap used for the reconstruction. She underwent resection of the free flap under general anesthesia. Interestingly, we found mucosalization and hyphae-like *Candida* on the histopathological examination. Regarding factors of cancerization, it is reasonable to consider causes that lead to chronic inflammation, such as mucosalization (alteration in the environment), external stimuli in the oropharyngeal area, or *candidasis*.

1. Introduction

The use of free flaps in the maxillofacial region, such as radial forearm free flaps and anterolateral thigh (ALT) flaps, for reconstruction after tumor resection, such as squamous cell carcinoma (SCC), has become the gold standard for the oral rehabilitation of patients [1]. These flaps allow better locoregional control in orofacial cancers and improve the functional and cosmetic outcomes. However, the number of reports on the occurrence of SCC in free flaps used for surgical reconstruction has been increasing. In these cases, it can be difficult to determine whether the carcinoma is a recurrence or a second primary carcinoma in the free flap. Furthermore, such carcinomas may be more prevalent among patients who undergo surgical reconstruction [2]. In the present study, we report the rare case of a patient who was diagnosed with a second primary carcinoma in a free flap used for reconstruction after

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segmental mandibulectomy in the oral cavity.

2. Presentation of case

A 59-year-old woman was referred to our department complaining of swelling in the lower gingiva in 2009. Her previous history included hypopharyngeal carcinoma for which she had undergone left oropharynx partial resection (without neck dissection) surgery and high-dose radiation therapy (up to 70 Gy). She had no history of cigarette smoking or alcohol consumption.

Regarding the clinical picture, her left gonial angle showed swelling and sequestration around the left first molar (Fig. 1-A, B). Our clinical diagnosis was osteoradionecrosis. The possibility of cancer recurrence could not be excluded based on contrast-enhanced computed tomography and magnetic resonance imaging. She underwent a biopsy, and the results showed inflamed granulation tissue with infection. She was administered regular debridement and antibacterial treatment as a conservative therapy. However, no improvement in the symptoms was observed with this conservative therapy. Therefore, she underwent left mandible segmental resection and grafting with an ALT flap in 2012 (Fig. 2-A). The histological diagnosis was osteoradionecrosis. The possibility of cancer was not found from findings the specimen. She was followed up at our outpatient clinic. In 2016, 4 years after the reconstruction surgery, the patient presented with exophytic swelling with leucoderma on the free flap (30 × 20 mm; Fig. 2-B). There was no regional lymphadenopathy. Based on the biopsy results, we diagnosed the patient with SCC of the left buccal mucosa. It was unclear if the tumor was present on a preoperative computed tomography image, because the image had a strong artifact due to the previous reconstruction surgery (data not shown). The patient underwent partial resection of the free flap under general anesthesia. Histopathological findings from the resected specimen confirmed that the carcinoma tissue showed irregular keratinization on the free flap side (Fig. 3-A, B). The border between the mucosa and free flap was clear at deeper levels, despite appearing unclear more superficially. The cancer cell nests were primarily localized within the free flap, and there were few cancer pearls in the oral mucosa (Fig. 3-C, D). According to these results, we diagnosed the patient with SCC derived from the free flap reconstruction. In addition, the p16 immunostaining was not positive (Fig. 4-B), and the cornfield layer revealed hyphae-like Candida (Fig. 4-A, C). The postsurgical course was uneventful, and there was no evidence of tumor recurrence in the 2-year postoperative follow up.

3. Discussion and conclusions

When SCC arises in a free flap, it is difficult to determine whether it is a recurrent or second primary carcinoma. Tokita et al. [2] have reported that to diagnose a second primary carcinoma arising in a free flap, the following conditions should be met: 1) the tumor should be limited to the free flap and be far from the oral mucosa; 2) there should be no tumor remnant after the initial treatment; 3) at

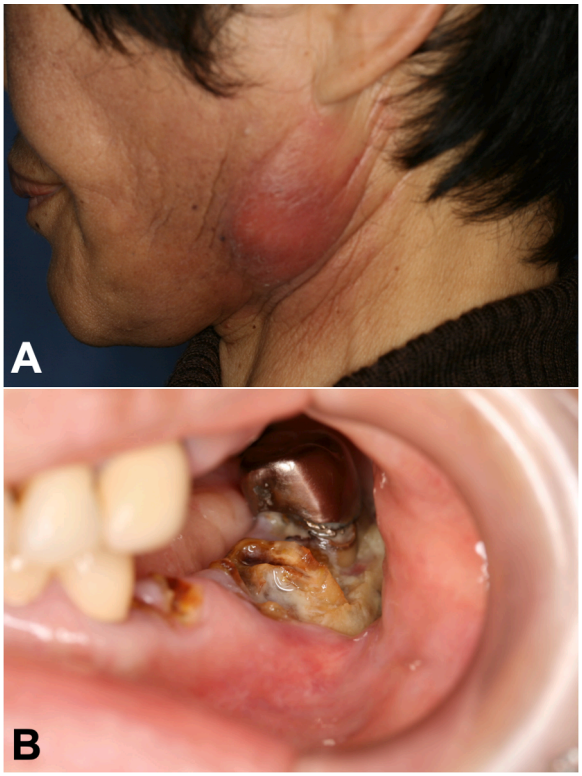

Fig. 1. Clinical photograph of the lateral face (A) and oral findings (B) at the initial visit.

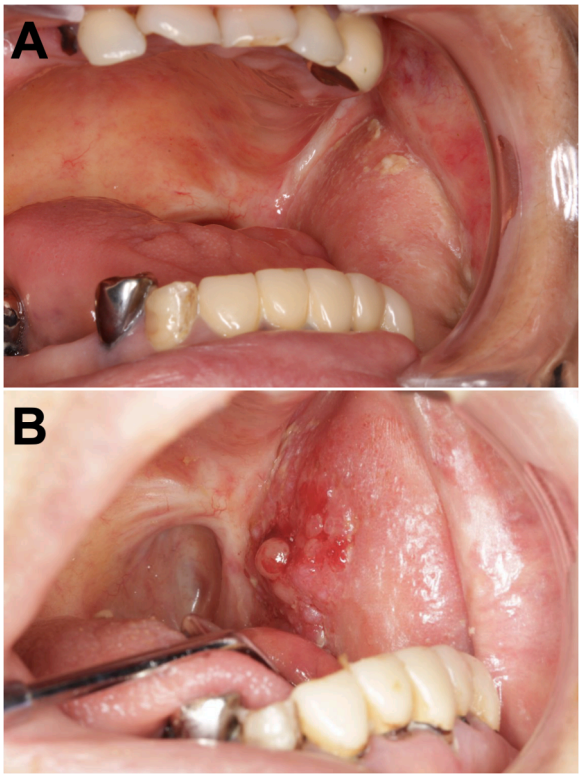

Fig. 2. Clinical photograph of the oral cavity after reconstruction using an anterolateral thigh flap (A) and the second primary carcinoma (B).

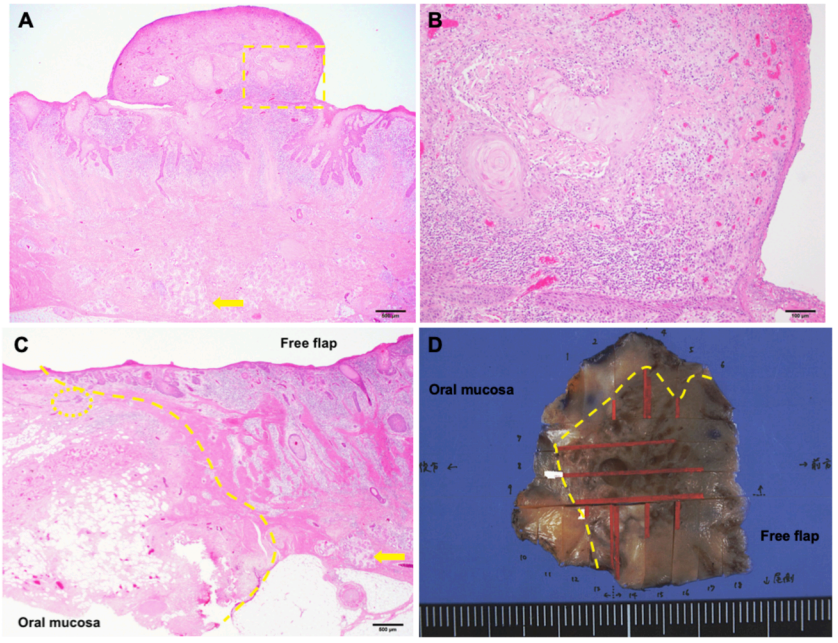

Fig. 3. A, Histological appearance of the lesion. Yellow arrow represents the sweat glands (hematoxylin-eosin staining, original magnification 20 ×). B, High powered image of the yellow box in A (original magnification 100 ×). C, Histological appearance of the border region between the oral mucosa and the free flap. Yellow arrow represents sweat glands (hematoxylin-eosin staining, original magnification 20 ×). D. The surgical specimen. The yellow line is the border between the oral mucosa and free flap. The red line is the squamous cell carcinoma range of invasion.

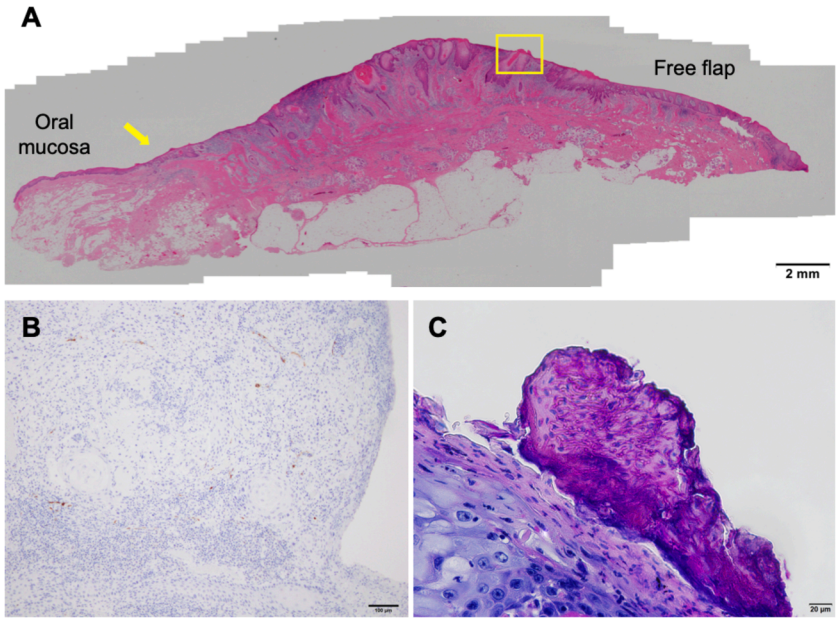

Fig. 4. A, Histological appearance of the lesion. The yellow arrow shows the border region between the oral mucosa and free flap (hematoxylin-eosin staining, original magnification 20 ×). B, p16 immunostaining showing negativity in the yellow box from Fig. 3-A (original magnification 100 ×).C. The cornfield layer revealed *Candida* using PAS staining in the yellow box from A (original magnification 400 ×).

least 3 years should have elapsed since the end of the initial treatment [3]; 4) SCC should be confirmed by histopathologic examination; and 5) there should be no skin malignancies elsewhere on the body [2]. In this case, the carcinoma met the conditions specified above. Therefore, we concluded that it was a second primary carcinoma, not a recurrence. Furthermore, the patient in our case underwent reconstruction for osteoradionecrosis, which constituted further evidence that the lesion was a second primary carcinoma. A review of the literature showed 20 similar cases that involved tumors that occurred in flaps used for reconstruction after resection of the oral cavity or head and neck cancers (Table 1). Among these cases, patients who underwent reconstruction ranged in age from 28 to 80 years (mean, 55 years), and the age at recurrence ranged from 61 to 88 years (mean, 69.3 years). These intervals ranged from 3.5 to 39 years (mean, 14.3 years). Interestingly, the characteristics of second primary cancers may be present regardless of the time that has passed since the reconstruction [3]. The ratio of male to female patients was 1.5:1 in these prior reports. Hypopharynx was most often seen at the expression site (5/20 cases). Radial forearm free flaps were most commonly used (7/20 cases) and the cancers were exophytic in most of these cases (10/17 cases). Histological diagnosis was SCC in all cases.

For the review, we also considered the suggested possible factors of second primary carcinoma (Table 2). Regarding smoking and drinking, 3/15 of the reported patients smoked and 3/14 used alcohol from the time of reconstruction to the time of recurrence. Ho et al. and Iseli et al. [4,5] indicated that these potential carcinogens were irrelevant because the smoking and alcohol habits had been stopped after the initial operation in their cases. Similar to our case, the patients in the previous reports had no drinking and smoking habits. However, there was history of smoking (11/16 cases) and drinking (9/15 cases) before reconstruction in more than half of all reported cases. From this, it can be inferred that second primary carcinoma may be associated with cigarette and alcohol use even if the patient had stopped using these substances before the reconstruction. Yoshino et al. [6] have described that carcinogenesis was related to the free flap being directly exposed to radiation. To this end, we found that patients underwent radiotherapy after reconstruction in 3/16 cases. Therefore, direct exposure of the free flap to radiation may be a carcinogenic factor. Other risk factors include anemia [6], human papilloma virus (HPV) [2], and *Candida* infection [2,20]. Yoshino et al. reported that the second primary carcinoma was related to anemia [6]. However, this has been confirmed in only two cases. Moreover, such cases were only found in Yoshino's et al. [6] report. Various authors have stated that the second primary carcinoma is associated with HPV; however, in our case, pathological findings did not reveal HPV-p16 presence with immunostaining. There has only been one previous report of HPV-p16 expressed in the tumor region [2]. Therefore, there may be a relationship between HPV-p16 and second primary carcinoma, but it is less common than other etiologies. Interestingly, *Candida* spp. was histopathologically-confirmed in three cases and mucosalization in eight cases in the free flap. Parkin [7] and Martel et al. [8] reported that approximately one in five cancers are caused by infection. *Candida* spp. are opportunistic pathogens where, depending on the local oral microenvironment or whether the host defense mechanisms are compromised, they can cause oral mucosal infections [9]. Moreover, the asymptomatic carriage rates of *Candida* spp. in healthy individuals range from 3 to 70% [10]. It stands to reason that patients following cancer surgery have compromised immunity compared with healthy individuals; therefore, candidiasis may develop. Samaranayake et al. [11] and Bartielt et al. [12] reported that leukoplakia with candidiasis has a higher rate of malignant transformation than uninfected leukoplakia, with approximately 15% of non-dysplastic chronic hyperplastic candidiasis progressing to dysplastic lesions, and 10% of these developing into oral SCC. Woolgar et al. [1] have reported that the cutaneous phenotypes of the free flap are maintained unless there is chronic candidiasis. Furthermore, it was suggested that when

Table 1
Cases of second primary carcinoma arising in the free flap.

Case number	Author	Gender	Reconstruction (Age)	Recurrence (Age)	Interval (Year)	Site	Type of reconstruction	Clinical appearance	Histology
1	Yoshino et al., 1989 [6]	F	65	74	9	Hypopharynx	Local skin flap, DP flap	Exophytic	SCC
2	Yoshino et al., 1989 [6]	F	72	78	6	Hypopharynx	Door flap	–	SCC
3	Yoshino et al., 1989 [6]	F	60	76	16	Hypopharynx	DP flap	–	SCC
4	Deans et al., 1990 [14]	M	37	61	24	Larynx	DP flap	Exophytic	SCC
5	Scott and Klassen, 1992 [15]	M	28	67	39	Floor of mouth	Acromiothoracic tube pedicle	Exophytic	SCC
6	Montgomery et al., 1993 [16]	M	52	58	6	Floor of mouth	PMMC flap	Ulcer	SCC
7	Sa'do et al., 1994 [17]	F	61	70	9	Buccal mucosa	Free skin flap	Shallow ulcer	SCC
8	Sakamoto et al., 1998 [18]	M	63	73	10	Hypopharynx	Radial forearm free flap	Scattered lesion	SCC
9	Ohtsuka et al., 1998 [19]	F	64	72	8	Lower gum/Upper gum	PMMC flap	Exophytic	SCC
10	Iseli et al., 2002 [5]	M	40	67	27	Larynx	DP flap	Exophytic	SCC
11	Monnier et al., 2008 [3]	M	58	62	3.5	Tonsil	Radial forearm free flap	Exophytic	SCC
12	Monnier et al., 2008 [3]	M	54	64	10	Tonsil/Transglottics	DP flap	White thickening	SCC
13	Ho et al., 2011 [4]	M	53	65	12	Tongue	PMMC flap	Necrotic nodule	SCC
14	Zemann et al., 2011 [20]	F	32	62	30	Palate cleft	Free skin flap	Exophytic	SCC
15	Yamasaki et al., 2011 [21]	M	70	75	5	Hypopharynx	Radial forearm free flap	Exophytic	SCC
16	Nasu et al., 2012 [22]	M	59	75	16	Tongue	Radial forearm free flap	Exophytic	SCC
17	Tokita et al., 2013 [2]	M	80	86	5.5	Lower gum	Radial forearm free flap	Erythroplakia	SCC
18	Cymerman et al., 2013 [23]	M	39	62	23	Floor of mouth	Radial forearm free flap	Hyper plastic nodule	SCC
19	Valentini et al., 2016 [24]	F	51	72	21	Tongue	Radial forearm free flap	White patch	SCC
20	Present case	F	62	67	5	Buccal mucosa	ALT flap	Exophytic	SCC

ALT: anterolateral thigh, DP: deltopectoral, F: female, M: male, PMMC: pectoralis major myocutaneous, SCC: squamous cell carcinoma.

Table 2
Possible risk factors of second primary carcinomas.

Case Number	Author	Until the reconstruction		After the reconstruction		Ra (Gy)	Mucosalization	Other
		Smoking	Drinking	Smoking	Drinking			
1	Yoshino et al., 1989 [6]					–	+	Anemia
2	Yoshino et al., 1989 [6]					40[a]		
3	Yoshino et al., 1989 [6]					64[a]		Anemia
4	Deans et al., 1990 [14]	+						
5	Scott and Klassen, 1992 [15]	–	–	+	+			
6	Montgomery et al., 1993 [16]	+	+	–	+	65		
7	Sa'do et al., 1994 [17]	–	–	–	–	40		
8	Sakamoto et al., 1998 [18]	+	+	–	+	–		
9	Ohtsuka et al., 1998 [19]					40.5		
10	Iseli et al., 2002 [5]	+	–	–	–	50		
11	Monnier et al., 2008 [3]	+	+	–	–	–	+	
12	Monnier et al., 2008 [3]	+	+	–	–	+	+	
13	Ho et al., 2011 [4]	+	+	–		60[a]	+	
14	Zemann et al., 2011 [20]	–	–	–	–		+	Candida
15	Yamasaki et al., 2011 [21]	+	+	–	–	–		
16	Nasu et al., 2012 [22]	+	+	+	+		+	
17	Tokita et al., 2013 [2]	+	+	–	–	–	+	Candida/HPV
18	Cymerman et al., 2013 [23]	+	+	+	+	–		
19	Valentini et al., 2016 [24]	–	–	–	–	–	+	
20	Present case	–	–	–	–	70	+	Candida

[a] The case underwent postoperative radiotherapy. HPV: human papilloma virus.

inflammation occurs in a free flap, there is colonization of the free flap surface by *Candida* species. This indicates that mucosalization of the free flap and cancerization are related to *Candida*. In our case, the presence of *Candida* spp. was confirmed inside the free flap surface but not the oral mucosa. This is because the skin flap surface is rougher than the oral mucosa; therefore, it may be easier for *Candida* to invade the skin flap. Furthermore, it is possible that maintaining oral hygiene is more difficult in patients who have undergone oral surgery than in healthy individuals. Taken together, it is considered that *Candida* accumulates more easily and may stimulate carcinogenesis in the oral region in patients after reconstruction surgery.

In addition, various clinicians have described other possible causes of second primary carcinoma arising in a free flap. Tokita et al. [2] have proposed several possible explanations for the generation of second primary tumors in free flaps. It is possible that the primary carcinoma was implanted into the flap at the time of the initial tumor resection. Alternatively, the second primary tumor was present in the flap before the initial operation. An alternative hypothesis is that the second primary carcinoma was induced by exposure of the free flap to new environmental conditions [13]. In our case, it cannot be assumed that the primary carcinoma was implanted into the flap at the time of initial tumor resection because our primary resection target was not a carcinoma but osteoradionecrosis. It is possible, but unlikely, that the second primary tumor was present in the flap before the initial operation. Therefore, the possible cause could be chronic inflammation, such as mucosalization, or an alteration in the environment, external stimuli in the oropharyngeal area, or *candidasis*.

Relatively few cases of second primary carcinomas arising in free flaps have been reported; therefore, we call for an increase in case reports that will aid future discussion regarding the incidence of second primary carcinomas in free flaps in the oral cavity.

Legal

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal.

Authors' contribution

The authors made substantial contributions to the present case series. MT, MS and YM contributed to the conception and design as well as writing the manuscript. AW provided clinical pathological photo documentation. SY and TY reviewed literature and contributed to the final drafting of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study was approved by the Institutional Review Board of the Faculty of Dentistry, Tokyo Medical and Dental University (No.1247).

Consent for publication

We have obtained the patient's permission for use of photographs. Consent for publication has been obtained.

Conflicts of interest

The authors declare that they have no competing interests.

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None.

List of abbreviations

ALT	anterolateral thigh
DP	deltopectoral
F	female
HPV	human papilloma virus
M	male
PMMC	pectoralis major myocutaneous
SCC	squamous cell carcinoma

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