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Case report

Development of new leukoplakias and leukoplakia-associated second/multiple primary oral cancers: A case report and literature review

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ABSTRACT

We present the case of a 39-year-old male primary leukoplakia patient who developed multiple new leukoplakias and multiple leukoplakia-associated primary oral cancers during a 20-year follow-up period. In addition, 9 previous studies involving primary leukoplakia patients, including six involving patients who developed new leukoplakias and three involving patients with second/multiple primary oral cancers, are reviewed. The tendency for primary leukoplakia patients to develop new leukoplakias and leukoplakia-associated second/multiple primary oral cancers after treatment is highlighted. Lifelong follow-up is recommended for patients with leukoplakia.

1. Introduction

The occurrence of second/multiple primary cancers in the oral cavity, pharynx, and larynx has been extensively studied in patients with oral squamous cell carcinoma [1–6]. In these previous studies, the incidence of second/multiple primary cancers was reported to range from 10 to 24%, and the 5-year survival rate of the patients who developed second/multiple primary cancers was significantly lower than that of the patients who did not develop these tumors [1,2]. About one-third of the second/multiple primary cancers arose in the oral cavity, which might have been partly due to the continuing exposure of the epithelial surface of the oral cavity to carcinogens such as those found in tobacco and alcohol [7]. In addition, Liao et al. reported that in Taiwan, an endemic area for betel quid chewing, the oral cavity was the predominant site of second/primary cancers in up to 70.3% of cases of oral squamous cell carcinoma, which was much higher than the frequencies found in other studies [2]. This suggests that environmental factors affecting the oral cavity such as tobacco/alcohol consumption and betel quid chewing, which can cause the development of precancerous oral lesions or primary oral cancer, also play a very important role in the development of second/multiple primary oral cancers.

Leukoplakia is the most common precancerous lesion affecting the oral cavity [8,9]. Tobacco use and dietary habits are some of the main causes of oral leukoplakia [10,11]. Silverman et al. reported that the frequency of malignant transformation in oral leukoplakia ranged from 0.13 to 17.5% [12,13]. Moreover, patients whose leukoplakias are surgically removed frequently develop local recurrence and new leukoplakias [14,15]. Meanwhile, a review of English literature reveals that 15.9–52.6% of patients with leukoplakia-associated primary oral cancer developed second/multiple primary oral cancers (Table 2); however, details on whether these second/multiple primary oral cancers were associated with new leukoplakias were not described in the literature. All these raise the question of whether patients with primary leukoplakia have a tendency to develop new leukoplakias and whether patients whose primary leukoplakia or whose new leukoplakia undergoes malignant transformation are at risk of developing second/multiple primary oral cancers.

Here, we report a case of leukoplakia that was followed-up for 20 years, during which time the patient developed multiple new leukoplakias, all of which developed subsequently second/multiple primary oral cancers. In addition, we have reviewed the literature involving primary leukoplakia patients who developed new leukoplakias or second/multiple primary oral cancers. The findings of the present study regarding the development of new leukoplakias and leukoplakia-associated second/multiple oral cancers in oral leukoplakia patients supports the use of a long-term follow-up policy in this patient group, which would allow the early detection

☆ AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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Table 1
New leukoplakias in follow-up oral leukoplakia patients reported in the English literature.

Author	Primary leukoplakia (cases)	Follow-up (months)	New leukoplakias (cases)	Frequency of new leukoplakias
Frame [14]	63	29	4	6.3%
Stich et al. [20]	111	6	15	13.5%
Chiesa et al. [16]	80	60	8	10%
Gooris et al. [21]	23	5.3	4	17.4%
Bagan et al. [22]	30	56.4	23	83.3%
Chiesa et al. [23]	170	60	14	8.2%

and management of second/multiple leukoplakia-associated primary oral cancers.

2. Case report

A 39-year-old male patient presented with a chief complaint of a white patch on the left side of his tongue, which was causing him discomfort, in 1992. He had a 25-year history of tobacco use, but no history of alcohol use. A physical examination revealed a white flat patch measuring about 10 mm × 12 mm in size situated on the left side of his tongue. The patient was scheduled for regular follow-up examinations. After three months, the white patch had not disappeared, and an excisional biopsy was performed to remove the whole of the white patch, in which the final pathological diagnosis was epithelial hyperkeratosis. Five years later (1997), second and third primary leukoplakias measuring 4 mm × 5 mm and 2 mm × 7 mm were found on the left and right sides of the floor of the mouth, respectively. The patient was followed-up every 3 months. In 1999, a fourth primary leukoplakia measuring 8 mm × 14 mm in size was found in the patient's palate, and a new white flat patch lesion was detected on the left side of the tongue near to the site of the primary lesion. The new patch lesion was larger than the original leukoplakia lesion observed in 1997. The leukoplakia on the left side of the tongue was surgically excised, and a free skin flap transplantation was performed. The excised tongue lesion was diagnosed as severe epithelial dysplasia. Biopsies of the palate and the floor of the mouth were performed to completely remove them, in which the final pathological diagnoses were severe epithelial dysplasia and squamous cell carcinoma, respectively. After treatment, the patient visited the outpatient department of our hospital for regular follow-up examinations. However, for various reasons, the patient did not visit our hospital for a check-up between 2000 and 2006, when he presented with a new white patch in his lower front gingiva measuring 4 mm × 6 mm in size, and a swelling sensation together with mixed red and white lesions in his palate. A CT examination showed that the left maxillary alveolar bone had been partially resorbed. Surgical excision of the left maxillary bone was carried out, with a final pathological diagnosis of squamous cell carcinoma. In 2010, the patient was found to have a non-painful red ulcer in his lower front gingiva, where the white patch was present 4 years previously. Local excision of the lower front gingiva and alveolar bone was performed, with a final pathological diagnosis of squamous cell carcinoma. During the 20-year follow-up period, according to his doctor's suggestion, the patient quit smoking but occasionally relapsed. At the time of last follow-up (2012), the patient was in good condition with no sign of recurrent leukoplakia or carcinoma. Now the patient is on regular follow-up.

3. Literature review

We used the PubMed and Google scholar databases to identify studies and cases relevant to the present study. The keywords used in our search were: new leukoplakia, metachronous leukoplakia, second leukoplakia, second primary oral cancer, multiple oral cancers, leukoplakia-associated oral cancer, and metachronous oral cancer. Cases from studies published by the same author with non-overlapping data were included.

In relation to the occurrence of new leukoplakia, 6 articles involving primary leukoplakia patients who developed new leukoplakias, published between 1985 and 2005, were included in the present study (Table 1). In these studies, the frequency of new leukoplakia ranged from 6.3% to 83.3%.

In relation to the occurrence of second/multiple primary oral cancers, 3 articles involving primary leukoplakia patients who developed second/multiple primary oral cancers, published between 1986 and 2004, were included in the present study (Table 2). In these studies, the frequency of second/multiple primary oral cancers ranged from 15.9% to 52.6%.

4. Discussion

Surgical excision, CO_2-laser surgery, and chemotherapeutic approaches such as the application of bleomycin or vitamin A can be effective treatments for leukoplakia [13–16]. However, even after successful primary therapy, 18.5% of leukoplakia patients suffer local recurrence, 16.2% of patients develop new leukoplakias (second primary leukoplakias), and 6.6% of patients develop oral carcinoma and other neoplasms at other sites [17]. The recurrence of leukoplakia and the development of new leukoplakias account for the majority of unfavorable events suffered by leukoplakia patients after primary therapy. Leukoplakia recurrence is easily detected because the changes at the primary site are the main focus of attention for patients and doctors during the follow-up period, whereas new leukoplakias that occur away from the primary site might be neglected [16–18]. Moreover, it is hypothesized that exposure to carcinogens leads to the independent transformation of multiple epithelial cells at different sites and the development of distinct lesions from several altered clones, resulting in the production of new dysplastic and malignant lesions [19]. Therefore, the development of new leukoplakias suggests that oral environmental factors might still be causing the dysplastic and/or malignant transformation of lesions, suggesting that patients with new leukoplakia are at high risk of developing oral squamous cell carcinoma. In the present case, the patient quit smoking but sometimes relapsed, and three new leukoplakias were observed at different stages of the 20-year follow-up period, all of which subsequently developed into carcinomas. In addition, as shown in Table 1, five of six studies showed that the frequency of new leukoplakia ranged from 6.3% to 17.4% [14,16,20,21,23], whereas the remaining study showed that 83.3% of the cases displaying a high frequency of new leukoplakia involved progressive high-risk proliferative verrucous leukoplakia [22]. These findings focus attention on the occurrence of new leukoplakia in patients after primary leukoplakia therapy, particularly in patients with primary proliferative verrucous leukoplakia, which has a strong tendency to develop into oral squamous cell carcinoma [24].

As shown in Table 2, 31.5–52.6% of the proliferative verrucous leukoplakia patients that developed primary oral cancer went on to develop second primary oral tumors in different areas of the oral cavity [24,25]. These proliferative verrucous leukoplakia-associated primary oral tumors did not often occur at the typical