

Original Article

Verrucous carcinoma associated with oral submucous fibrosis that gradually transforms to squamous cell carcinoma: a rare case report

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Abstract: Oral verrucous carcinoma (OVC) is a distinct variant of well differentiated oral squamous cell carcinoma (OSCC). It usually occurred in old patients ranged from 50 to 80 years with a male predominance. Metastasis to lymph nodes or distant organs is rare. Oral submucous fibrosis (OSF), a premalignant condition of oral cavity, has been reported to associate with the development of OSCC and rare cases of OVC. However, very few cases of VC associated with OSF that transforms into OSCC have been reported. We present here a rare case of OVC associated with OSF that gradually transform to OSCC, which may shed light on the development and progression of OVC. Our study showed evidence suggested that verrucous carcinoma may arise from the potentially malignant lesions and gradually transform to a high malignant tumor with a propensity for metastasis.

Keywords: Oral verrucous carcinoma (OVC), oral squamous cell carcinoma (OSCC), oral submucous fibrosis (OSF), malignant transformation, lymph node metastasis

Introduction

Verrucous carcinoma (VC) is a well-differentiated variant of squamous cell carcinoma characterized by slow invasive growth and low incidence of metastasis. It usually occurred in old patients ranged from 50 to 80 years with a male predominance. The most usual site of occurrence is oral cavity, accounting for 75% of cases involved [1]. Metastasis to lymph nodes or distant organs is rare. Previous study indicated that oral verrucous carcinoma (OVC) may arise from previous lesions like oral leukoplakia, proliferative verrucous leukoplakia, and so on [2]. The higher prevalence of leukoplakia has been reported among patients with oral submucous fibrosis (OSF) [3]. Most recently, the study by Komal et al. has indicated that OSF may be the reason for the development of OVC [4]. The development of OSCC has been reported to occur in one-third of the OSF patients [5]. However, the development of VC in such patients is comparatively rare. Here we reported a rare case of OVC initially presented with the oral leukoplakia and mild OSF. During the

next two years, the patient suffered from several times of local recurrence and cervical lymph node metastasis in the last recurrence, even after extended resection. Histopathological analysis demonstrated OVC that gradually transformed to squamous cell carcinoma and contributed to the malignant behavior of the disease.

Case report

This study was approved by the ethnic review committee of the Xiangya Stomatological Hospital, Central South University, and informed consent was obtained from the patient. A 49-year-old male patient came to our hospital with the major complain of a mass present on the right labial mucosa for the past 3 years. The patient was a cigarette smoker for about 30 years (10 cigarettes a day). He had chewed betel nuts for 15 years (5 pieces a day). Three years ago, the patient developed a protruding lump on the right labial mucosa. Initially the growth was of soy bean size with slight hardness and tenderness. There were no obvious



Figure 1. Prutruding cauliflower-sized lump in the right retromolar area.

volume expansion and patient received no treatment. Two years ago, he developed a painless white growth on the right of spat mucosa, which expanded slowly. About half a year ago, a protruding cauliflower-like growth was present in the right retromolar area (**Figure 1**). The patient denied any other significant medical history.

Intraoral examination showed poor oral hygiene status (dental calculus grade II) with limited mouth opening (1.5 cm). Physical examination showed a 2×3.5 cm white filamentous projection in the right angulus oris mucosa and a 3×3.5 cm white cauliflower-like lump present in the right buccal fat pad extending towards pterygomandibular medial ligament. An incisional biopsy was taken. Histopathological analysis showed oral leukoplakia with mild epithelial dysplasia and mild OSF in right retromolar area (**Figure 2A** and **2B**). The pathological diagnosis was compatible with verrucous carcinoma and OSF. The expanded surgical excision was performed with segmental mandibular resection and platysma flap reconstruction. Tissue was submitted for microscopic examination. The histopathologic examination showed parakeratinised stratified squamous epithelial lesions characterized by verrucous hyperplasia (**Figure 2C**). The epithelium showed rete ridges infiltrated to the connective tissue and formed the typical “pushing” border (**Figure 2D**). There was no invasion in bone tissue. Lack of atypia and intact basement membrane ruled out conventional Oral Squamous Cell Carcinoma (OSCC). Thus final diagnosis of OVC was given. Patient left hospital with good condition and recovered mouth opening.

Four months later, the patient presented with painless white induration below the right angulus oris. For the further treatment, the patient admitted to hospital six months later. Physically the patient was good in condition with good spirit, appetite, sleep, and defecation. Patient’s mouth opening was 2.3 cm. Two white protruding patches could be seen close to the angulus oris. The patient underwent local excision and reconstruction with a local tissue flap. The excisional showed cell nests with a definite atypical character (**Figure 2E** and **2F**). Clinicopathological analysis confirmed the diagnosis of OVC.

Ten months later, the patient admitted to our hospital the third time with the local recurrence of disease. The patient reported that a small lump was observed two months ago in the right labium, with no efficiency of anti-inflammatory therapy. About 1 month ago, another lump appeared in his right buccal area. The lesion increased greatly in size, and became tender and firmer in consistency. The patient was given anti-inflammatory therapy locally for 1 week and the pain was partially alleviated. He was in fair condition when came to our hospital. Clinical examination showed facial asymmetry due to swelling of labia and verrucous projection in the right angulus oris. Under the right side of the angulus oris and buccal area, a 3×4 cm growth was presented. On palpation, the lesion was tender and firm in consistency. The ipsilateral submandibular lymphnodes were palpable. The patient was treated with the buccal and labial resection plus suprahyoid lymph node resection. Submental lymph node was palpable during the surgery and showed lymph node reactive hyperplasia. Histopathological diagnosis was verrucous carcinoma with focal squamous cell carcinoma (**Figure 2G** and **2H**).

Over a month after the third operation, the patient felt pain in his right ear and lower area and a broad-bean-sized nodule was identified. The growth increased gradually and expanded to the table-tennis size, along with the increased pain and hardness in texture. Three months later, the patient was hospitalized for the fourth time with the unbearable pain. He described poor appetite, weight loss, and sleep difficulty. Clinical examination showed month opening of 2 cm with a 4×3 cm growth identified in right submandibular region. The lesion was hard in texture, tenderness on palpable with well-delin-

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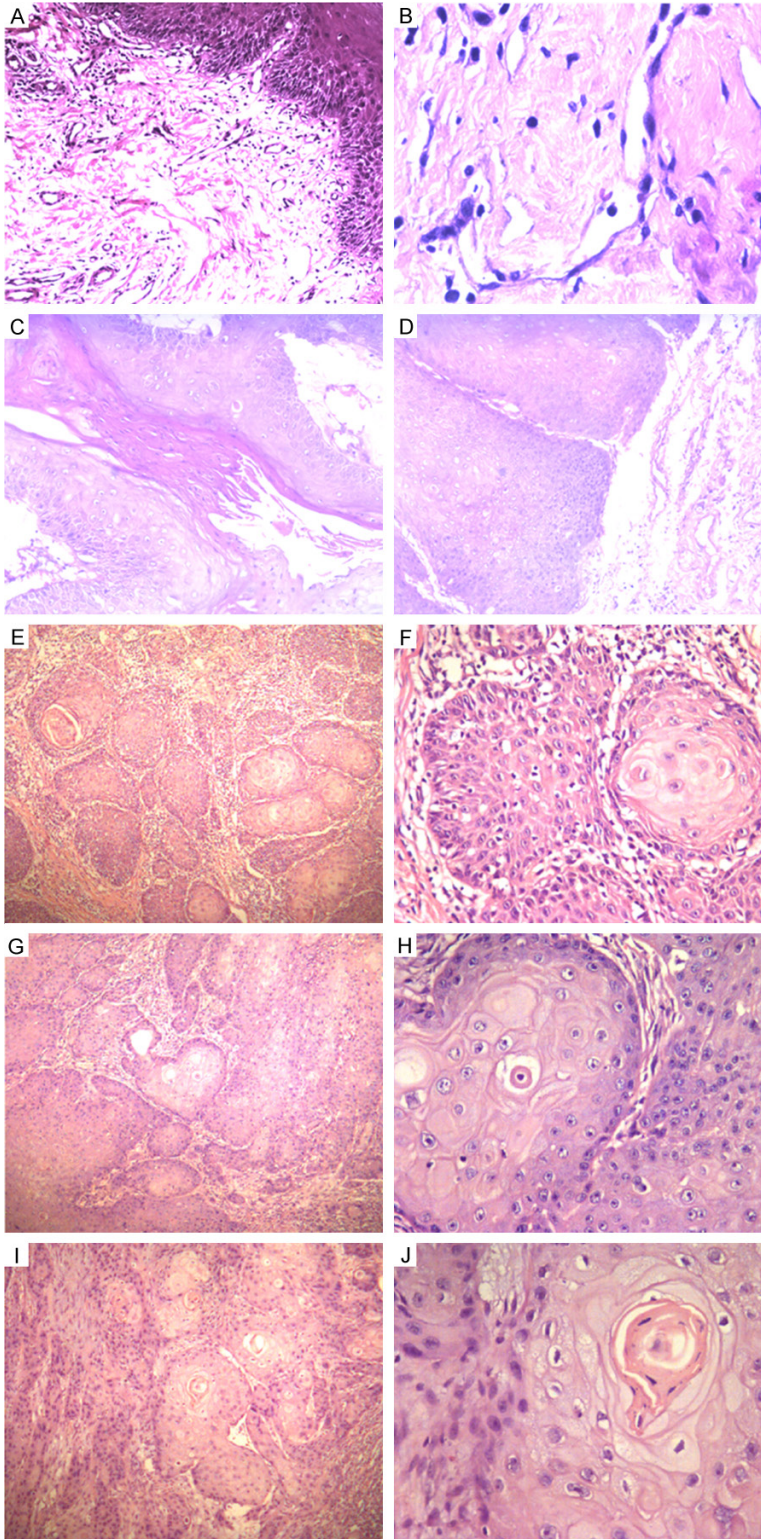


Figure 2. Histopathological analysis of OVC associated with oral submucous fibrosis that gradually transforms to squamous cell carcinoma. Mild oral submucous fibrosis can be seen in submucosa of retromolar area (A and B, HE, A×200, B×400); Parakeratinised stratified squamous epithelial lesions characterized by verrucous hyperplasia. Rete ridges infiltrated to the connective tissue and formed the typical “pushing” border. The basement membrane

is integrity with chronic inflammatory cell infiltration in the sub-epithelial connective tissue. (C and D, HE, ×200); There were cell nests in the right buccal fat pad with certain atypia (E and F, HE, E×100, F×400); Verrucous carcinoma with focal high-differentiation squamous carcinoma that characterized by marked cellular atypia and karyokinesis (G and H, HE, G×100, H×400); (G) High-moderate differentiated squamous cell carcinoma with a keratin pearl in the centers. High-moderate differentiated squamous cell carcinoma with cellular atypia and karyokinesis visible (I and J, HE, I×100, J×400).

eated margin and poor mobility. Radical neck dissection and bilateral commissurotomy were further performed. Histopathological examination demonstrated the high-moderate differentiated squamous cell carcinoma in right submandibular tumor with the right cervical lymph node metastasis (**Figure 2I** and **2J**). About a month later, the patient presented with recurrent tumor behind the right ear. He left the hospital without any treatment and died 8 months later.

Discussion

OVC is a rare tumor of older people that generally accepted as slow growing, locally aggressive and rarely metastasizes. The exact etiology of OVC is not well established. Smoking or tobacco chewing and betel nut chewing are the causative factors. Oral submucous fibrosis (OSF) or leukoplakias have also been reported to act as a predisposing factor [2]. OSF has long been established as a precancerous condition [6] and chewing betel nut has proved to be the main cause

[7]. Patients accompanied with oral leukoplakia or lichen planus have been suggested to contribute to the malignant transformation of OSF [8]. In this case, the patient had a history of smoking for more than 30 years and chewed betel nut nearly 15 years, and was initially diagnosed with oral leukoplakia and mild OSF, which in turn gradually malignantly transformed to OVC. The mild epithelial dysplasia was observed in our subject, which has also been found to significantly associate with malignant transformation of oral mucosal disorders [9].

The OSF has been reported to associate with development of OSCC in one third of patients, the occurrence is considered to be extremely rare [5]. By contrast, there were very few cases of OSF-associated OVC reported, and OSF, as a premalignant condition caused by chewing betel nuts, has been suggested to contribute to the development of OVC [4, 7]. This finding is consistent with the results reported in our study, which indicated the malignant transformation of OSF into OVC. OVC has been long considered as a low malignant tumor with a propensity for local invasion but rare metastasis [10]. Lymph node and distant metastasis are rare. Surgery is generally considered as the primary treatment for OVC with a good prognosis [11]. However, the repeated local recurrences of the OVC have been reported [12], and the radiation therapy prescribed has been suggested to provoke anaplastic transformation of VC [13]. In our case, OVC patient showed the repeated recurrence even after the expanded resection without radiation therapy, which in turn progressed into lymph node metastasis. Histopathological analysis demonstrated the anaplastic transformation of OVC into SCC after several recurrences and lymph node metastasis of the disease. Transformation of OVC into OSCC has been reported microscopically [14]. Anaplastic transformation of VC into OSCC has been reported to happen in 20% of patients, and cervical lymph node metastasis was estimated to occur in 45.5% of OSCC [15, 16]. These may partially elaborate the aggressive behaviors observed in our study and few cases of OSF-associated OVC reported. All these results indicated that OSF may lead to the development of OVC, which may further transform into OSCC that causes the metastasis of the disease.

To sum up, our study showed a rare case of OVC that may arise from OSF and gradually trans-

form to OSCC, which may shed light on the development and progression of OVC. Our study showed evidence suggested that verrucous carcinoma may arise from the potentially malignant lesions and gradually transform to a high malignant tumor with a propensity for metastasis. However, the potential reason and under what condition this transformation happened and the potential management strategies are still unknown and need further investigation.

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Disclosure of conflict of interest

None.

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