Multiple Verrucous Carcinomas of the Oral Cavity

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Abstract The author herein reports a case of multiple verrucous carcinomas (VCs) of the left lower gingiva. A 78-year-old man was admitted to our hospital because of gingival tumor. A biopsy revealed severe dysplasia. Surgical resection was performed. Grossly, there were three verrucous lesions (25, 20, 10 mm) in the left lower gingiva. Histologically, 2 tumors (4, 2 mm) were found in addition to the grossly visible 3 tumors. All the 5 tumors were VCs. The tumors showed verrucous and papillary proliferation of squamous epithelium with little cellular atypia. No invasive features were recognized. The dermis showed lymphocytic infiltration. The surrounding mucosa showed many broad foci of squamous cell carcinoma in situ and severe dysplasia (high grade intraepithelial neoplasm). Gradual merges between the VCs and squamous cell carcinoma in situ or severe dysplasia were frequently recognized. Immunohistochemically, the VC tumor cells and squamous lesions were negative for human papilloma virus antigens. P53 protein was expressed in all the VCs and squamous epithelial lesions: it was accentuated in the basal and suprabasal cells of VC. Ki-67 antigen was also expressed in the 5 VCs and in the squamous lesion, and Ki-67 labeling index ranged from 8 to 16 % in VC and from 37 to 62 % in the squamous lesions. These data support the multicentric nature of VC and that the severe dysplasia–carcinoma in situ sequence have been proposed in the etiology of VC.

Keywords Oral cavity · Verrucous carcinoma · Pathology · Histology · Immunohistochemistry

Introduction

Verrucous carcinoma (VC) (Ackermann's tumor) is a rare type of low-grade, well differentiated squamous cell carcinoma, and develops mainly in the skin, genitalia, esophagus, and oral cavity. The pathogenesis of VC of the oral cavity is still obscure, but is thought to be associated with human papilloma virus (HPV) [1–3], poor oral hygiene, chewing of tobacco, and use of snuff. Several studies of VC of the oral cavity have been reported [4–6]. All of them are solitary VC, and multiple VCs of the oral cavity have not been reported, to the best of the author's knowledge. Three cases of multiple VCs of other sites have been reported [7–9].

Case Report

A 78-year-old farmer consulted our hospital complaining of gingival tumors. He had no familial history of oral neoplasms. He was a smoker and an alcoholic (14 g/day). His medical history showed diabetes mellitus (68 years) and hypertension (72 years), and was being treated by antidiabetic and antihypertensive drugs. He and his wife had no risk for HPV infection. He was negative for human immunodeficiency virus. Oral examination revealed three verrucous tumors in the left lower gingiva, and a biopsy revealed severe dysplasia. Surgical resection was performed.

Grossly, there were three verrucous lesions (25, 20, 10 mm) in the left lower gingiva (Fig. 1). The author examined 17 sections. Histologically, 2 tumors (4, 2 mm) were found in addition to the grossly visible 3 tumors. All the five tumors were VCs. The five tumors are shown in Fig. 2. All the tumors showed verrucous and papillary

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Fig. 1 Gross findings of the resected left lower gingival specimen. There were three verrucous tumors (arrows)

Fig. 3 Individual keratinization is recognized in the verrucous carcinoma. The cellular atypia is minimal. HE, ×200

Fig. 2 Low power view of verrucous carcinomas. Verrucous proliferation of squamous epithelium is evident. The cellular atypia is mild or minimal. **a** The 25 mm tumor. **b** The 4 mm tumor

Fig. 4 The basal cell and suprabasal cells show mild atypia in a verrucous carcinoma. Lymphocytic infiltration is seen in the dermis. HE, ×200

proliferation of squamous epithelium with little cellular atypia (Fig. 3). There were individual keratinization and squamous pearl formations (Fig. 3). The basal and suprabasal layer showed a little cellular atypia (Fig. 4). No invasive features were recognized. The dermis showed lymphocytic infiltration.

The surrounding mucosa showed many broad foci of squamous cell carcinoma in situ (Fig. 5) and severe dysplasia (Fig. 6) (high grade intraepithelial neoplasm). Direct transition between dysplasia and squamous cell carcinoma in situ was observed. In addition, direct gradual merges between the VCs and squamous cell carcinoma in situ or severe dysplasia were frequently recognized (Fig. 7).

Fig. 5 Squamous cell carcinoma in situ in non-verrucous carcinoma areas. There are cellular atypia, loss of polarity, mitotic figures, individual keratinization, loss of differentiation, and apoptotic bodies are seen. HE, ×200

Fig. 7 Direct transition between verrucous carcinoma and squamous cell carcinoma in situ. The squamous element is squamous cell carcinoma in situ. HE, ×200

Fig. 6 Severe dysplasia in non-verrucous carcinoma areas. Atypical cells with hyperchromatic nuclei and with loss of polarity occupy the lower five sixths of the squamous layer. HE, ×200

Fig. 8 Ki-67 labeling is high in the basal and suprabasal cells in a verrucous carcinoma. ×100

An immunohistochemical study was performed with the use of Dako Envision method, as previously reported [10, 11]. The antibodies were HPV (polyclonal, Dako), p53 protein (DO7, Dako), and Ki-67 (MIB1, Dako). Immunohistochemically, the VC tumor cells and squamous lesions (squamous cell carcinoma in situ + severe dysplasia) were negative for human papilloma virus antigens. P53 protein was expressed in all the 5 VCs and squamous epithelial lesions; it was accentuated in the basal and suprabasal cells of VC. Ki-67 antigen was also expressed in the 5 VCs and in the squamous lesion, and Ki-67 labeling index ranged from 8 to 16 % in VC (Fig. 8), and from 37 to 62 % in the squamous lesions.

The margins of the resected specimen were negative for VC, but positive for severe dysplasia. The patient was treated by it excision or vaporization and low-dose radiation. The patient is now being followed up 11 months after the operation.

Discussion

The tumors of the present case showed verrucous proliferation of squamous epithelium with little cellular atypia. No invasion was seen. The histology of the present tumors fulfills the criteria of VC. VCs of the present case are different from verrucous hyperplasia, proliferative verrucous

leukoplakia, and well differentiated papillary squamous cell carcinoma with regard to the histology and immunohistochemistry [12]. Verrucous hyperplasia and verrucous leukoplakia are not true neoplasms and do not show florid verrucous proliferation as seen in the present case. These diseases are usually negative for p53 and show low Ki67 labeling. Papillary squamous cell carcinoma has more atypia and p53 and Ki67 labeling are more strong and high.

Of particular interest is that the present case showed multiple VCs. Five VCs were recognized in the present case. There are 3 reports of multiple VCs in other organs [7–9]. However, there are no reports of multiple VCs in the oral cavity. The present findings indicate that multiple VCs can occur in the oral cavity.

Also, of particular interest is that the present case showed carcinoma in situ and severe dysplasia (high grade intraepithelial neoplasm) in the non-VC areas. In addition, there were merges between VCs and the squamous cell carcinoma in situ and severe dysplasia. In general, dysplasia–carcinoma in situ sequence is considered to play an important role in the squamous cell neoplasms, such as uterine cervix and esophagus. Therefore, it is very likely that severe dysplasia and squamous cell carcinoma sequence gave rise to the VCs in the present case. The concept that the squamous lesions are lateral spread of VCs is unlikely. This hypothesis has not been proposed in the pathogenesis of VC. The present case lacked histological evidence for viral infection such as inclusion body and koilocytosis. In addition, HPV was negative in the immunohistochemical investigation. Therefore, the HPV appears not to be the cause of the VCs in the present case. However, exact HPV status in the present case is unclear, because no nested PCR for HPV DNA was performed in the present case. According to Fujita et al. [1], HPV DNA was detected in 11/23 (48 %) in oral VCs by the use of PCR genotyping. Studies of HPV DNA may be required in the present case.

The expression of p53 protein and Ki-67 antigen in VC has been reported [13, 14, 15, 16, 17]. The present case showed p53 protein in all VCs and squamous lesions, and its expression was accentuated in the basal cells of VC and in all the layers of the squamous lesions. Similar tendency was observed in Ki-67 antigen. The expression of p53 and relatively high Ki-67 labeling support the low grade malignant nature of the VCs of the present case, and suggest the true preneoplastic and neoplastic nature of the squamous cell carcinoma in situ and severe dysplasia.

These data of the present case support the multicentric nature of VC and that the severe dysplasia–carcinoma in situ sequence has been proposed in the etiology of VC.

Conflict of interest The author has no conflict of interest.

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