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CASE REPORT

Verrucous carcinoma of the buccal mucosa: histopathological, cytological and DNA-cytometric features

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We describe a patient with an exophytic oral lesion diagnosed as verrucous carcinoma. The lesion existed without metastases, at least 5 years. Local excisions led to recurrences and continuous expansion. Scalpel biopsies for histopathological and polymerase chain reaction examination were obtained from characteristic regions of the lesion. Brush biopsies for exfoliative cytology (EC) were taken, in order to screen the mucosal area covered by the lesion. After Feulgen restaining of the smears, nuclear DNA contents were measured using a TV image analysis system. An exophytic lesion of the buccal mucosa was diagnosed as low-grade malignant through histopathology and EC combined with DNA-image cytometry (peritetraploid DNA-aneuploidy). Due to almost normal microscopic appearance of the epithelium of verrucous carcinoma, thorough cytological/DNA-cytometric and histological examinations are needed. Brush biopsies of such neoplastic oral lesions showing DNA-aneuploidy with peritetraploid stemlines should be used for diagnosis and follow-up examination of these patients.
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Description of the case

In March 2005, a 69-year-old Caucasian female came to the department of oral surgery with an exophytic lesion of the buccal mucosa, which existed at least 5 years, growing slowly and causing no pain. The lesion extended from the right commissural angle of the mouth to the uvula, floor of the mouth and right lateral border of the tongue, showing a whitish erythematous hyperplastic surface (Fig. 1). The patient reported no smoking habits and also that local excisions performed in the last years in a department of oral and maxillofacial surgery, caused more aggressive and quicker regrowth of the lesion. No local or systemic metastases were reported after thorough examination with computerized tomography of head and neck, lung and abdomen.

The first histopathological examination was performed in September 2000 and showed a squamous cell papilloma without signs of malignancy. The next scalpel biopsy was taken in May 2001 and revealed an initial verrucous carcinoma. At that time and after excising the focal area of squamous cell carcinoma, a remodelling operation was carried out in order to reduce the size of the lesion and comfort the patient, because a total excision was very difficult due to its extended size. Afterwards and until December 2004 six more scalpel biopsies were taken in order to clarify the dignity of the lesion, which were all negative for malignancy. In March 2005, the histopathological examination performed in our department revealed an early invasive carcinoma (Table 1).

In order to further clarify the nature of the lesion, we performed seven brush biopsies for cytological examination in a period of 4 weeks (two brush biopsies on 11th March and five on 11th April). Each of the brush biopsies was taken from different areas of the lesion eventually covering the whole lesion. Furthermore, a large incisional biopsy (at least 3×1 cm) was taken from a characteristic area (arrow in Fig. 1) for histopathological evaluation (Table 1). A small part of the biopsy was deep frozen in liquid nitrogen and sent to a commercial institute (Laboratoriumsmedizin und Mikrobiologie, Prof. Arndt & Partner, Hamburg, Germany) for examination for the presence of 92 established types of HPV.

The first cytological diagnosis resulting from the brush biopsies on 11th March was doubtful for tumour cells revealing slight cellular atypia. Because of this fact DNA-image cytometry was performed, which showed an aneuploid/peritetraploid DNA distribution with a dominant stemline around 4c and a lower stemline

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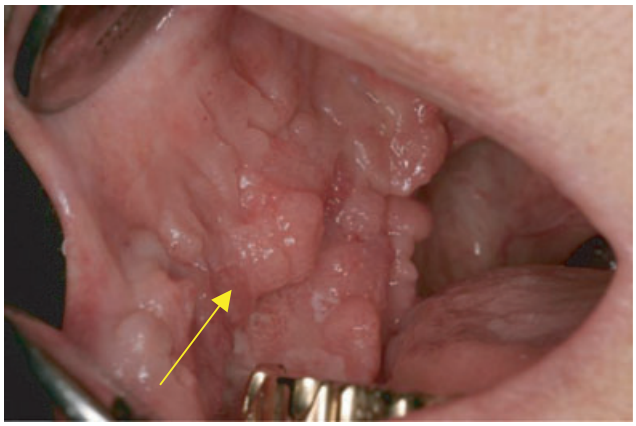

Figure 1 Clinical appearance of a verrucous carcinoma. Arrow shows localization of scalpel biopsy.

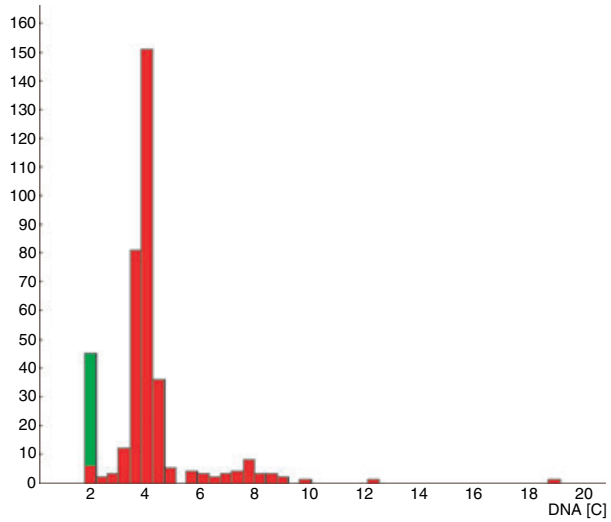

Figure 2 Peritetraploid aneuploid DNA histogram of the lesion in Fig. 1 (dominant DNA-stemline around 4c and three cells with DNA content >9c).

Table 1 Incisional biopsies of the exophytic lesion, performed in the last 5 years

Date of the incisional biopsy	*Result*
22.09.2000	Squamous cell papilloma of the oral mucosa with chronic inflammation
10.05.2001	Initial verrucous carcinoma
28.05.2001	Histological specimen after remodelling surgery: no malignancy/no inflammation
21.06.2001	Reactive inflammatory mucosal lesion of traumatic cause; no malignancy
10.10.2001	Reactive inflammatory mucosal lesion; no signs of recurrence/no malignancy
12.12.2003	Reactive inflammatory mucosal lesion; no signs of recurrence/no malignancy
24.06.2004	Reactive inflammatory mucosal lesion with papillomatosis; no signs of recurrence/no malignancy
10.12.2004	Reactive inflammatory mucosal lesion; no signs of recurrence/no malignancy; candidiasis?
16.03.2005	Early invasive verrucous carcinoma

around 2c. The brush biopsies taken 4 weeks later revealed suspicion of cancer (regressive, atypical squamous cells with pycnotic and disordered nuclei and increased nuclear–cytoplasmic ratio) and DNA-image cytometry showed once more a peritetraploid/aneuploid DNA-stemline and three cells with a DNA content >9c (Fig. 2).

The histopathological examination finally proved the diagnosis of an invasive verrucous carcinoma (Fig. 3), polymerase chain reaction showed no signs of HPV infection.

The purpose of this report was to describe a case of verrucous carcinoma of the buccal mucosa, which has been diagnosed through histopathological, cytological and DNA-cytometric examination. It is our opinion that the characteristic cytological/DNA-cytometric features should be kept under consideration in further similar cases, so that a thorough examination of such lesions can be made.

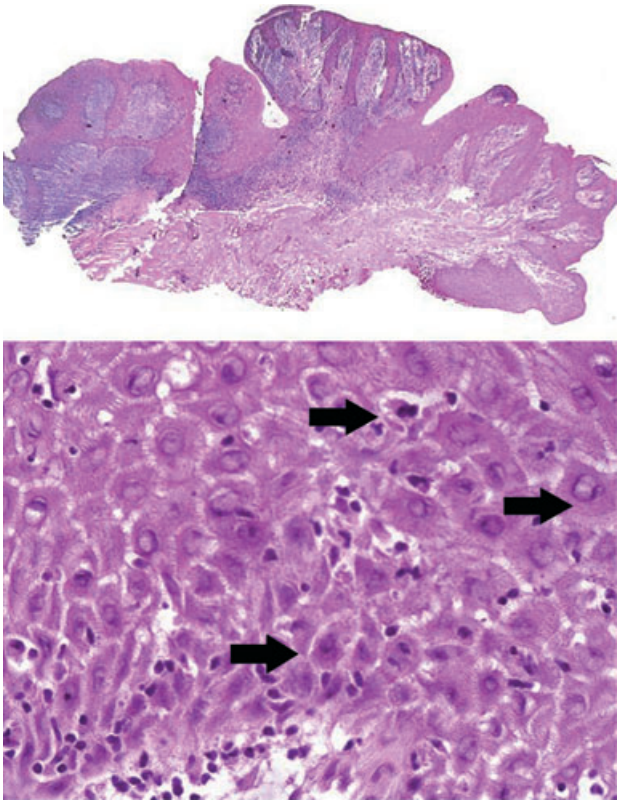

Figure 3 Verrucous carcinoma consisting of keratinocytes with large atypical nuclei (arrows; 40× and 400× respectively).

Comments

Diagnosis of verrucous carcinomas can be difficult and is normally based on histopathological examination of clinically suspicious oral lesions, which are being characterized by exophytic overgrowth and a locally destructive pushing tendency against the connective

tissue, without metastatic tendency. It is usually very extended, existing at least 2 or 3 years, before a definite diagnosis can be made. Proliferative verrucous leukoplakia (high-risk pre-cancer) represents its precursor although many cases are closely associated with the use of smokeless tobacco or spit-tobacco (snuff dipper's cancer; 1, 2). Literature shows that in many cases of Ackerman's tumour the final diagnosis can be established only after many years and multiple, deep incisional biopsies, which may reveal foci of conventional squamous cell carcinomas within a verrucous carcinoma. Therefore, such lesions must be evaluated from experienced pathologists and should be treated as squamous cell carcinomas (1, 3, 4).

As already proven in clinical practice, exfoliative cytology (EC) combined with DNA-image cytometry can early detect oral cancer and its recurrence and also predict the prospective behaviour of oral dysplastic lesions (5–7). Furthermore, Hemmer and Kraft (8) could show that oral lesions, which progressed to verrucous carcinoma, revealed DNA-aneuploidy after flow cytometric examination and maintained an abnormal aneuploid cell line through the whole follow-up period. The authors mentioned above (5–8) conclude that DNA-aneuploidy is a common marker for the early diagnosis of both verrucous and squamous cell carcinomas.

Our case report revealed an aneuploid/peritetraploid DNA distribution through EC and DNA-image cytometry of a histologically verified verrucous carcinoma of the buccal mucosa. This abnormal DNA distribution in combination with the history of the patient and the clinical features should lead both the clinician and the cytopathologist to a strong suspicion of an Ackerman's tumour. Considering the difficulty of setting the cytological diagnosis in such cases, the cytopathologist should search for parts of the smear (or rather of the lesion) which show DNA-aneuploidy and particularly cells with DNA content $>9c$, in order to reveal foci of squamous cell carcinomas, which should further be examined through histopathology, so that false-negative diagnoses can be avoided.

Furthermore, peritetraploid DNA distributions of the oral mucosa should be considered as DNA-aneuploid, thus as neoplastic and raise the suspicion of an Ackerman's tumour. If the macroscopic appearance is exophytic, screening of the complete area of these lesions through brush biopsies including DNA-cytometry could reveal focal areas of medium- or high-grade squamous cell carcinoma.

In conclusion, exophytic oral lesions which raise the suspicion of malignancy should be examined both with EC combined with DNA-image cytometry and histopathology, in order to minimize the risk of false-negative diagnoses.

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