Oral Oncology EXTRA (2006) 42, 85–90

ELSEVIER

ORAL ONCOLOGY EXTRA

http://intl.elsevierhealth.com/journal/ooex

CASE REPORT

Hybrid verrucous carcinoma of the oral cavity: A challenge for the clinician and the pathologist

Rita A. Depprich [a,*], Jörg G. Handschel [a], Claus U. Fritzemeier [a], Rainer Engers [b], Norbert R. Kübler [a]

[a] *Department of Cranio- and Maxillofacial Surgery, Heinrich-Heine-University Duesseldorf, Moorenstrasse 5, 40225 Duesseldorf, Germany*
[b] *Department of Pathology, Heinrich-Heine-University Duesseldorf, Moorenstrasse 5, 40225 Duesseldorf, Germany*

Received 8 September 2005; accepted 11 September 2005

KEYWORDS
Oral cavity carcinoma;
Oral verrucous carcinoma;
Hybrid verrucous carcinoma

Summary Verrucous carcinoma (VC) a low-grade variant of squamous cell carcinoma (SCC) with specific clinical, morphologic and cytokinetic features is amongst the rarest of all oral cancers. A hybrid VC is a non-verrucous SCC that arises synchronously with the VC. We report a case of a monstrous exophytic tumor in the oral cavity. Histologic examination revealed distinct discrepancy to clinical observation. After review of the literature pathogenesis, histopathology and therapeutic options are discussed. The differential diagnosis of VC remains difficult and requires clinical and pathologic data confrontation. As the malignant behaviour of hybrid VC is confined to the non-VC component, careful examination of these tumors is recommended.

Background

Verrucous carcinoma (VC) first described in 1948 by Lauren V. Ackerman[1] is a form of squamous cell carcinoma with specific clinical, morphologic and cytokinetic features.[2] The term VC refers to those exophytic mucosal or cutaneous squamous tumors that are heaped above the epithelial surface with a papillary micronodular surface[3] and pushing margins. Most tumors involving the upper aerodigestive tract are found in the oral cavity with the glottic larynx being the most frequent nonoral site.[4] VC representing 2–12% of all oral cancers is mainly found in elderly men and closely aligned with the use of tobacco.[5,6] Other irritants to the oral mucosa such as bethel nut chewing, poor dental hygiene and Human Papilloma Virus (HPV) infection have been implicated in the development of oral VC.[3] To date histological evaluation remains a problem as benign microscopic appearance is controversal to the tumor's destructive clinical behavior. This

* Corresponding author. Tel.: +49 211 81 18181; fax: +49 211 81 18877.
E-mail address: depprich@med.uni-duesseldorf.de (R.A. Depprich).

1741-9409/$ - see front matter
doi:10.1016/j.ooe.2005.09.006

report describes a monstrous exophytic tumor in the oral cavity that emerged a hybrid VC.

Case report

The patient was a 73-year-old female from Yugoslavia with a history of diabetes and hypertension, but no history of alcohol or nicotin when she first came to our department in January 2004 complaining about a supposed 7 month existing swelling of the upper lip.

Clinical examination revealed an exophytic tumor extending all along the upper lip and a second similar smaller tumor on the right lower lip. In the oral cavity the tumor covered almost all the right palate and the right buccal mucosa and had infiltrated the upper and the lower lip (Fig. 1).

X-ray of the paranasal sinus showed basal clouding of the right maxillary sinus and destruction of the right upper alveolar arcus. Preoperative CT scan showed the enormous extension of the tumor with infiltration of the right hard palate and the right cheek mucosa and destruction of the maxillary anterior and lateral septum (Fig. 2). Additional PET revealed the huge size of the tumor but showed no suspicious lymph nodes.

Several biopsies from the oral cavity and upper lip revealed a well differentiated verrucous tumor.

Surgical treatment consisted of the resection of half of the right hard and soft palate, half of the right lower lip and the total upper lip. Reconstruction was performed using a modification of the

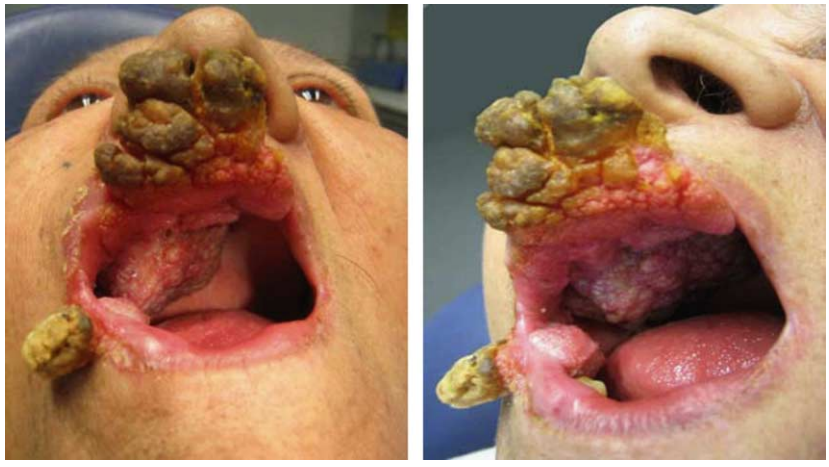

Figure 1 Preoperative view: an exophytic tumor extending all along the upper lip and a smaller tumor on the right lower lip. In the oral cavity the tumor covered almost all the right palate and the right buccal mucosa.

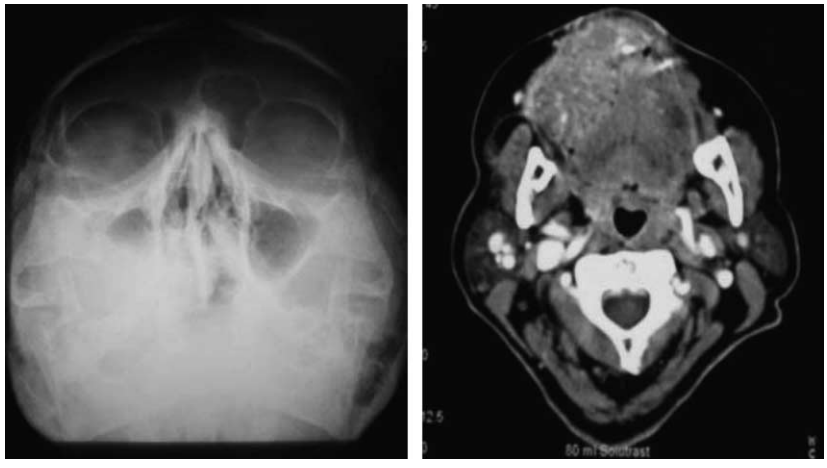

Figure 2 Preoperative X-ray (left): showing basal clouding of the right maxillary sinus and destruction of the right upper alveolar arcus. Axial CT scan showing tumor mass in the right palate (right).

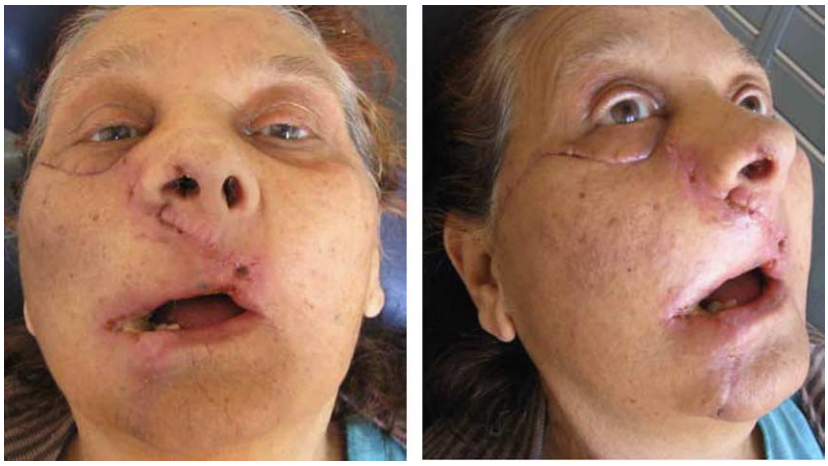

Figure 3 Postoperative view after resection of half of the right hard and soft palate, half of the right lower lip and the total upper lip. Facial reconstruction with a modification of the Esser flap, reconstruction of the upper lip with intraoral mucosa, maxillary defect reconstruction with a split skin.

Esser flap. The upper lip was reconstructed using intraoral mucosa and the defect resulting from partial resection of the maxilla was covered with a split skin graft and a temporary prosthesis (Fig. 3).

The histopathological examination revealed a verrucous squamous tumor (8.3 cm in diameter) (Fig. 4A—F) that only partly exhibited marked keratosis (Fig. 4A). In some parts the tumor showed additional endophytic growth (Fig. 4B and C) with sharply demarked pushing borders (Fig. 4D) and a moderate lymphoplasmocytic inflammatory host reaction (Fig. 4D). In these parts of the tumor the squamous epithelium lacked cytologic atypia (Fig. 4D), but at a distinct site slight cytological atypia became evident and the tumor exhibited unambiguous invasion of the stroma (Fig. 4E and F). Based on this the tumor was classified as a verrucous leukoplakia with focal progression into a highly differentiated SCC (pT1, pNX, pMX, G1, R0). After presentation of the clinical findings to the pathologist the final histological diagnosis of a hybrid VC arising from a proliferative verrucous leukoplakia was made.

In December 2004 a tissue sample from a 3 mm suspicious exophytic area of right lower lip presented recurrence of the high differentiated verrucous squamous cell carcinoma.

The planned surgical therapy could not be performed as the patient had a crippling apoplectic stroke and broke up coming to our department.

Discussion

VC first described in 1948 by Lauren V. Ackerman is a distinct variant of differentiated SCC with low grade malignancy, slow growth and no or only low metastatic potential.[2,7,8] It is often associated with long-term use of smokeless tobacco although examples occur among nonusers.[6,9] Bethel nut chewing, poor dental hygiene and Human Papilloma Virus (HPV) infection have been implicated in the development of oral VC.[3] The tumor representing 2—12% of all oral cancers mainly occurs in older men (Koch et al. detected median age at diagnosis 69.0 years,[3] although many cases have also been documented in older woman in areas where the habit of snuff dipping has been popular among women (e.g. West Virgina).[5,6] Verucous carcinoma in association with lichen planus have been reported.[10,11]

With respect to the upper aerodigestive tract, where the VC most often arises, the oral cavity, particularly the cheek mucosa, gingivae and retromolar areas, remains the most common site of origin.[12] The tumor may also be found on different sites including skin,[13] paranasal sinus,[14] bladder and anorectal region,[15] male and female genitalia,[16,17] sole of the foot,[3] and ear.[18]

Macroscopically the VC shows up an exophytic, broadly implanted tumor fungating in aspect with a warty or papillary surface. The histological appearance is described as highly differentiated squamous tumor covered by a thick keratinized layer arranged in deeply invaginated folds with a typically inflammatory reaction in the stroma composed of lymphocytes, plasma cells and histiocytes that tend to delimit the tumor mass.[19,20] The sharply circumscribed deep margin is often characterized as ''pushing border''.[21] The benign microscopic appearance is controversal to the tumor's destructive clinical behavior, although lymph node

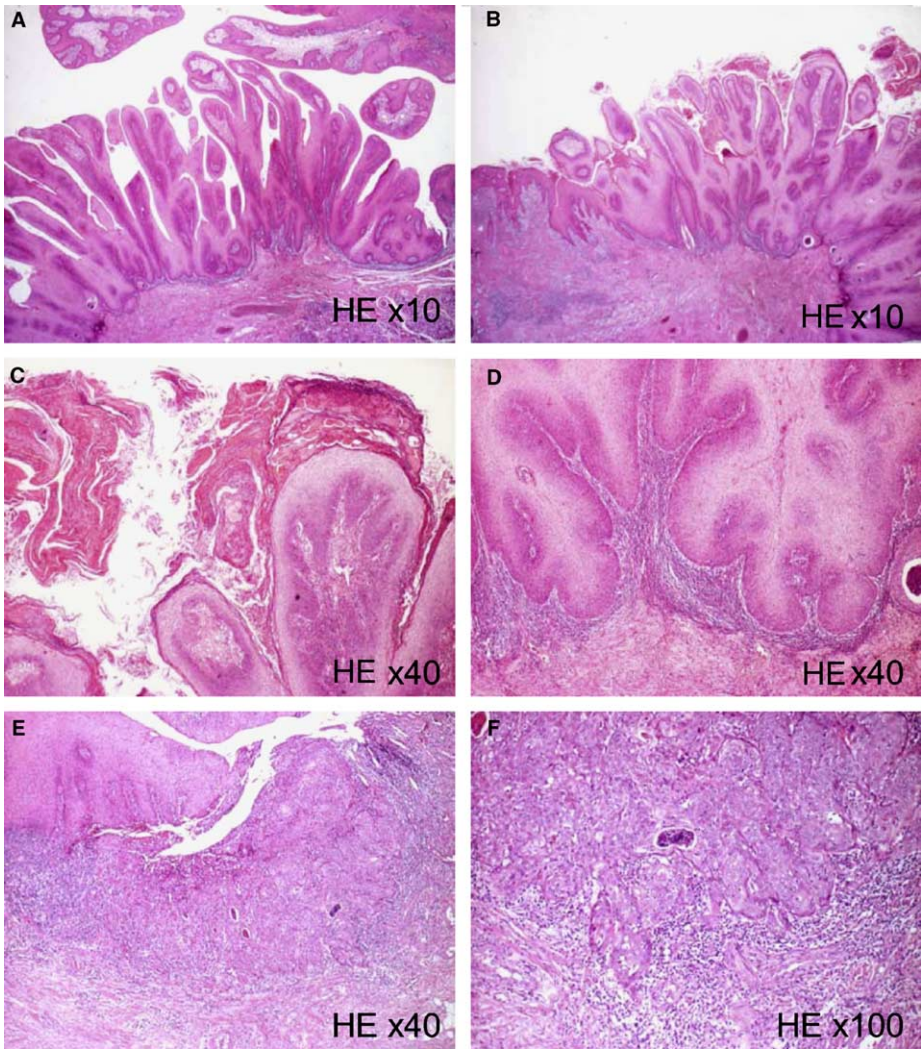

Figure 4 Histological characteristics. (A) Verrucous tumor showing a predominantly exophytic papillary growth pattern with only little keratinisation and a mild inflammatory host reaction. (B) Other parts of the verrucous tumor exhibiting exo- and endo-phytic growth characteristics with marked keratinisation (C), pushing borders (D), a dense lymphoplasmocytic inflammatory host response (D) and a lack of cytological atypia (D). (E) Classical highly differentiated squamous cell carcinoma with unambiguous invasion of the adjacent stroma and slight cytological atypia (F).

metastasis is not characteristic. The microscopic aspect ranges from benign squamous hyperplastic lesion to SCC.[4]

The etiology of VC remains unclear. The role of Human papillomavirus (HPV) infections in the etiology of verrucous lesion of the skin and genitalia is well documented, and HPV may also play an important role in the development of VC.[22,23] The results of a meta-analysis of 94 reports indicate that HPV is 2—3 times more likely to be detected in precancerous oral mucosa and 4.7 times more likely to be detected in oral SCC. The likelihood of detecting HPV in VC was found to be 29.5% and 46.5% in oral SCC.[24]

The development of VC from proliferative lesions makes it likely that the tumor develops from a benign precursor.[25] Thus, Hansen et al. described 10 histologic stages of proliferative verrucous leukoplakia,[26] ranging from a persistant and slow-growing benign unifocal, homogenous leukoplakia to a less differentiated squamous cell carcinoma. Batsakis et al. reduced the number of histologic stages to the following four: clinical flat leukoplakia without dysplasia, verrucous hyperplasia, VC, and conventional SCC.[27]

The histologic similarity between verrucous hyperplasia and VC is so close that some authors consider verrucous hyperplasia as a morphologic variant of VC.[28] Batsakis et al. regard verrucous hyperplasia as an irreversible precursor of VC and recommend the same treatment.[27]

No obvious differences between VC and well-differentiated SCC were found in proliferative activity of tumor cells as evaluated by PCNA labeling index or in p53 protein expression. However positive expression of CD44v9 was detected clearly more often in VC compared to well-differentiated squamous cell carcinoma, which might provide an explanation for the low incidence of lymph node metastasis in oral VC.[29]

Difficulties remain as to the appropriate classification of those lesions with dominant features of VC which also contain small foci of squamous cell carcinoma. In 20% of VC coexistent foci of less-differentiated SCC could be found.[21] A non-verrucous SCC (of varying degree and differentiation) that arises synchronously with the VC and in the same microscopic fields is defined by Batsakis et al. as a ''hybrid VC'',[4] which must be separated from papillary squamous carcinoma.[20,23,30]

Wide surgical excision is recommended as treatment of choice, since some studies suggested that anaplastic transformation of the tumor can occur after radiotherapy.[3,4,31] However other authors reported that the response of VC to radiotherapy is comparable to that of SCC.[32–35] Batsakis et al. believe that the hybrid carcinoma may be the carcinoma responsible for the phenomena of post-radiation 'anaplastic transformation'. They hypothesize the biologic course of such a hybrid malignancy to be that of the non-VC.[27]

Operative treatment of VC should not include neck dissection, even though enlarged lymph nodes may be palpated.[19]

Recently successfull treatment of an extensive VC with intra-arterial infusion of methotrexate[36] or topical 5-aminolevulinic acid-mediated photodynamic therapy was reported.[37]

No matter what the treatment is, the rate of local recurrences is said to be high ranging from 30% to 50%[7,31,33,38] and not unusually is the result of inadequate surgery because of the size of the tumor and left dysplasia close to the verrucous carcinoma.[7,39]

In our case the patient offered typically clinical features of a VC: a monstrous fungating tumor of the oral cavity with local destruction of the adjacent anatomical structures but no hint of lymph node mestastasis. Also in our case the histological classification of the verrucous tumor was difficult as the histologial appearance of different verrucous lesions is overlapping. Therefore, after presenting the clinical findings as well as the anamnestic informations of initially multifocal lesions in the absence of tobacco consumption to the pathologist, the final diagnosis of a hybrid VC, arising from a proliferative verrucous leukoplakia, was made. We hypothesize that the local recurrence after almost one year gives evidence of the premalignant potential of the mucosa as VC is very often linked with such premalignant alterations of the mucous membrane.

Conclusion

The differential diagnosis of VC remains difficult and requires clinical and pathological data confrontation. As the malignant behaviour of hybrid VC is confined to the non-VC component, careful examination of these tumors is recommended.

References

1. Ackerman LV. Verrucous carcinoma of the oral cavity. *Surgery* 1948;**23**:670–8.
2. Steffen C. The man behind the eponym: Lauren V. Ackerman and verrucous carcinoma of Ackerman. *Am J Dermatopathol* 2004;**26**(4):334–41.
3. Koch BB, Trask DK, Hoffman HT, et al. National survey of head and neck verrucous carcinoma: patterns of presentation, care, and outcome. *Cancer* 2001;**92**(1):110–20.
4. Batsakis JG, Hybels R, Crissman JD, Rice DH. The pathology of head and neck tumors: verrucous carcinoma, Part 15. *Head Neck Surg* 1982;**5**(1):29–38.
5. Montjean F, Evrard L, Magremanne M, et al. Oral verrucous carcinoma. *Rev Med Brux* 2004;**25**(3):173–7.
6. Bouquot JE. Oral verrucous carcinoma. Incidence in two US populations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;**86**(3):318–24.
7. Rink B. Verrucous carcinoma of the oral mucosa. *Laryngo-rhinootologie* 1991;**70**(10):542–5.
8. Tornes K, Bang G, Stromme Koppang H, Pedersen KN. Oral verrucous carcinoma. *Int J Oral Surg* 1985;**14**(6):485–92.
9. Neville BW, Day TA. Oral cancer and precancerous lesions. *CA Cancer J Clin* 2002;**52**(4):195–215.
10. Warshaw EM, Templeton SF, Washington CV. Verrucous carcinoma occurring in a lesion of oral lichen planus. *Cutis* 2000;**65**(4):219–22.
11. Castano E, Lopez-Rios F, Alvarez-Fernandez JG, et al. Verrucous carcinoma in association with hypertrophic lichen planus. *Clin Exp Dermatol* 1997;**22**(1):23–5.
12. Spiro RH. Verrucous carcinoma, then and now. *Am J Surg* 1998;**176**(5):393–7.
13. Brownstein MH, Shapiro L. Verrucous carcinoma of skin: epithelioma cuniculatum plantare. *Cancer* 1976;**38**(4): 1710–6.
14. Paleri V, Orvidas LJ, Wight RG, Bradley PJ. Verrucous carcinoma of the paranasal sinuses: case report and clinical update. *Head Neck* 2004;**26**(2):184–9.
15. Schwartz RA. Verrucous carcinoma of the skin and mucosa. *J Am Acad Dermatol* 1995;**32**(1):1–21, quiz 22-4.
16. Elliott GB, Macdougall JA, Elliott JD. Problems of verrucose squamous carcinoma. *Ann Surg* 1973;**177**(1):21–9.
17. Kraus FT, Perezmesa C. Verrucous carcinoma. Clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. *Cancer* 1966;**19**(1):26–38.
18. Proops DW, Hawke WM, van Nostrand AW, et al. Verrucous carcinoma of the ear. Case report. *Ann Otol Rhinol Laryngol* 1984;**93**(4 Pt 1):385–8.

19. Ferlito A, Recher G. Ackerman's tumor (verrucous carcinoma) of the larynx: a clinicopathologic study of 77 cases. *Cancer* 1980;**46**(7):1617—30.
20. Ferlito A, Devaney KO, Rinaldo A, Putzi MJ. Papillary squamous cell carcinoma versus verrucous squamous cell carcinoma of the head and neck. *Ann Otol Rhinol Laryngol* 1999;**108**(3):318—22.
21. Medina JE, Dichtel W, Luna MA. Verrucous-squamous carcinomas of the oral cavity. A clinicopathologic study of 104 cases. *Arch Otolaryngol* 1984;**110**(7):437—40.
22. Miller CS, White DK. Human papillomavirus expression in oral mucosa, premalignant conditions, and squamous cell carcinoma: a retrospective review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;**82**(1):57—68.
23. Suarez PA, Adler-Storthz K, Luna MA, et al. Papillary squamous cell carcinomas of the upper aerodigestive tract: a clinicopathologic and molecular study. *Head Neck* 2000;**22**(4):360—8.
24. Miller CS, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982—1997. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;**91**(6):622—35.
25. Ishiyama A, Eversole LR, Ross DA, et al. Papillary squamous neoplasms of the head and neck. *Laryngoscope* 1994;**104**(12):1446—52.
26. Hansen LS, Olson JA, Silverman Jr S. Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol* 1985;**60**(3):285—98.
27. Batsakis JG, Suarez P, el-Naggar AK. Proliferative verrucous leukoplakia and its related lesions. *Oral Oncol* 1999;**35**(4):354—9.
28. Slootweg PJ, Muller H. Verrucous hyperplasia or verrucous carcinoma. An analysis of 27 patients. *J Maxillofac Surg* 1983;**11**(1):13—9.
29. Ogawa A, Fukuta Y, Nakajima T, et al. Treatment results of oral verrucous carcinoma and its biological behavior. *Oral Oncol* 2004;**40**(8):793—7.
30. Batsakis JG, Suarez P. Papillary squamous carcinoma: will the real one please stand up? *Adv Anat Pathol* 2000;**7**(1):2—8.
31. Demian SD, Bushkin FL, Echevarria RA. Perineural invasion and anaplastic transformation of verrucous carcinoma. *Cancer* 1973;**32**(2):395—401.
32. Vidyasagar MS, Fernandes DJ, Kasturi DP, et al. Radiotherapy and verrucous carcinoma of the oral cavity. A study of 107 cases. *Acta Oncol* 1992;**31**(1):43—7.
33. Schwade JG, Wara WM, Dedo HH, Phillips TL. Radiotherapy for verrucous carcinoma. *Radiology* 1976;**120**(3): 677—9.
34. Jyothirmayi R, Sankaranarayanan R, Varghese C, et al. Radiotherapy in the treatment of verrucous carcinoma of the oral cavity. *Oral Oncol* 1997;**33**(2):124—8.
35. Nair MK, Sankaranarayanan R, Padmanabhan TK, Madhu CS. Oral verrucous carcinoma. Treatment with radiotherapy. *Cancer* 1988;**61**(3):458—61.
36. Sheen MC, Sheu HM, Lai FJ, et al. A huge verrucous carcinoma of the lower lip treated with intra-arterial infusion of methotrexate. *Br J Dermatol* 2004;**151**(3): 727—9.
37. Chen HM, Chen CT, Yang H, et al. Successful treatment of an extensive verrucous carcinoma with topical 5-aminolevulinic acid-mediated photodynamic therapy. *J Oral Pathol Med* 2005;**34**(4):253—6.
38. Shear M, Pindborg JJ. Verrucous hyperplasia of the oral mucosa. *Cancer* 1980;**46**(8):1855—62.
39. Aytekin A, Ay A, Okumus Y, Aytekin O. Reconstruction of an oral cavity defect resulting from verrucous carcinoma with a prefabricated parietal galeal flap. *Ann Plast Surg* 2003;**50**(1):106—7.