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Squamous cell carcinoma of the tonsillar region and the base of the tongue: a morphological and immunohistochemical comparative pilot study

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Abstract

Sixteen squamous cell carcinomas of the tonsillar region and 13 carcinomas of the base of the tongue were studied in a search for significant differences between the tumours of these two oropharyngeal subsites, which are known to carry a significantly different prognosis. The characteristics of the tumour cells and the tumour–host relationship were scored on H & E-stained slides, as well as on slides stained with a panel of antibodies. The results obtained were cross-tabulated and analysed with respect to the subsite. Ten variables were tested: cytonuclear pleomorphism, mitotic activity, the presence of atypical mitoses, keratinization, tumour grade, presence of eosinophils, severity of inflammatory response, and the expression of keratin-10, blood group antigens and collagen IV. When split up by site, only cytonuclear pleomorphism revealed a significant difference, tonsillar carcinomas more often exhibiting marked pleomorphism ($p = 0.04$).

Despite having some prognostic relevance for squamous cell carcinomas of the head and neck, the variables tested could not provide an explanation for the difference in biological behaviour of the tumours studied.

Key words: Tonsillar carcinoma; Base of the tongue carcinoma; Immunohistochemistry

Introduction

The oropharynx has often been considered to embody one single anatomical and physiological entity. Oncologically, however, this is questionable: of the five subsites that are recognized in the oropharynx, i.e. the posterior wall, lateral wall, soft palate and uvula, the tonsillar region and the base of the tongue, the latter two host as many as 95 per cent of oropharyngeal tumours (Smith *et al.*, 1963). Interestingly, cancers of these two subsites differ widely in clinical outcome, treatment results and survival rates, generally being more favourable in tonsillar carcinomas (Gelinas and Fletcher, 1973; Fayos, 1981; Baris *et al.*, 1983; Fayos and Morales, 1983; Bataini *et al.*, 1989; Mak-Kregar *et al.*, 1990; Hussey *et al.*, 1991) than in carcinomas of the base of the tongue (Gelinas and Fletcher, 1973; Fayos, 1981; Baris *et al.*, 1985; Hussey *et al.*, 1991; Jaulerry *et al.*, 1991; Mak-Kregar *et al.*, 1992). In the recently published material from our institute (Mak-Kregar *et al.*, 1990; 1992; 1993). These differences could not be explained by differences in patient characteristics, macroscopic features or treatment aspects.

To gain further insight into the biological behaviour of tumours of these two subsites, we decided to investigate several histopathological parameters which presumably have prognostic significance in head and neck carcinomas: cytonuclear pleomorphism (Jakobsson *et al.*, 1973; Goldsmith *et al.*, 1987), mitotic activity (Jakobsson *et al.*, 1973; Anneroth and Hansen, 1984; Quade and Loebe, 1984), presence of atypical mitoses (Quade and Loebe, 1984; Goldsmith *et al.*, 1987), keratinization (Bauer, 1974), peritumoural inflammatory response (Anneroth and Hansen, 1984) and the mode of tumour invasion (Jakobsson *et al.*, 1973; Anneroth and Hansen, 1984; Goldsmith *et al.*, 1987). We also wanted to study the histological grade, which is considered an important indicator of the biological behaviour of the tumours (Broders, 1920; Bauer, 1974; Loebe and Quade, 1982; Quade *et al.*, 1983; Quade, 1984; Quade and Loebe, 1984; Anneroth *et al.*, 1986; Goldsmith *et al.*, 1987), despite the fact that tumour grades are not well standardized, and therefore prone to intra- and inter-observer variability. In an attempt to overcome these shortcomings, we have reviewed the slides using a standardized checklist for all the above mentioned characteristics.

The development of monoclonal antibody technology (Mabs) and diagnostic immunohistochemistry has provided new possibilities in tumour diagnosis (Sikora, 1981; Ranken *et al.*, 1987). In stratified epithelia and in some squamous cell carcinomas, early keratinization can be visualized with monoclonal antibodies to cytokeratin-10 (K_{10}). Expression of K_{10} is thus expected to correlate to some extent to the differentiation grade of squamous cell carcinoma (Huszar *et al.*, 1986; Broers *et al.*, 1987). Loss of expression of blood group (A, B and H) antigens has been associated with increased tumour aggressiveness in malignancies of several sites, such as the urinary bladder

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(Sadayhi *et al.*, 1982) and oral mucosa (Dabelsteen *et al.*, 1983). Collagen IV staining can be employed to demonstrate the basement membrane that separates normal epithelia and the underlying surrounding mesenchymal tissue; discontinuity or even complete loss of basement membrane is seen in some carcinomas.

Since many monoclonals and antisera are applicable on formalin-fixed, paraffin-embedded material (Reibel *et al.*, 1985; Ivanyi *et al.*, 1989a), the previously obtained clinical results and archival material (biopsy specimens) can be approached from a new viewpoint.

This pilot study was conducted to explore the possibilities of relating retrospectively collected clinical data with histological findings using reevaluated H & E and immunohistochemically-stained slides. In addition, we attempted to assess morphological differences between the tumours in the two oropharyngeal subsites, that may possibly be related to their known different biological aggressiveness.

Materials and methods

Patients

This pilot study is based on a group of 29 patients (16 with tonsillar and 13 with base of the tongue carcinoma), out of a total of 162 patients (94 with tonsillar and 68 with base of the tongue carcinoma), who were admitted for primary treatment to the Netherlands Cancer Institute between 1966 and 1985 and followed for minimally three years or until death. A detailed description of all patients, classification methods and treatment was published previously (Mak-Kregar *et al.*, 1990, 1992, 1993).

The vast majority of patients in both groups were treated using external radiotherapy (86 and 90 per cent respectively). The 94 patients with tonsillar carcinomas had a significantly higher tumour control rate (61 per cent at three years) and overall survival (58 per cent) than the 68 patients with base of the tongue carcinomas (three years tumour control, 39 per cent; survival, 36 per cent; $p = 0.007$ and 0.004, respectively). The two groups of patients were similar with respect to possible prognostic factors: age, sex, intoxications, previous radiotherapy, TNM classification, radiation dose, size of radiation fields and overall treatment time. Significant differences between the two subsites were found only in the mean patient delay (three months in tonsillar carcinoma *versus* four and a half months in base of the tongue carcinoma, $p<0.05$) and in the incidence of patients with other severe disorders on admission (14 *versus* 28 per cent, respectively; $p<0.05$). However, it seems unlikely that these parameters alone would not account for the difference in tumour control rates, because they did not correlate significantly with the tumour size on admission, or with the choice of therapy (Mak-Kregar *et al.*, 1990, 1992, 1993).

This study is based on 29 patients in whom the pretreatment biopsy specimens of the primary tumour were readily available for a complete histopathological and immunohistochemical analysis. This subgroup has comparable patient characteristics, macroscopic tumour features and treatment as we reported in our former papers (Mak-Kregar *et al.*, 1990, 1992).

Twenty-two patients were males and seven were females, with a median age of 70 (31–87) years. The T-classification was as follows: five T1, seven T2, 12 T3

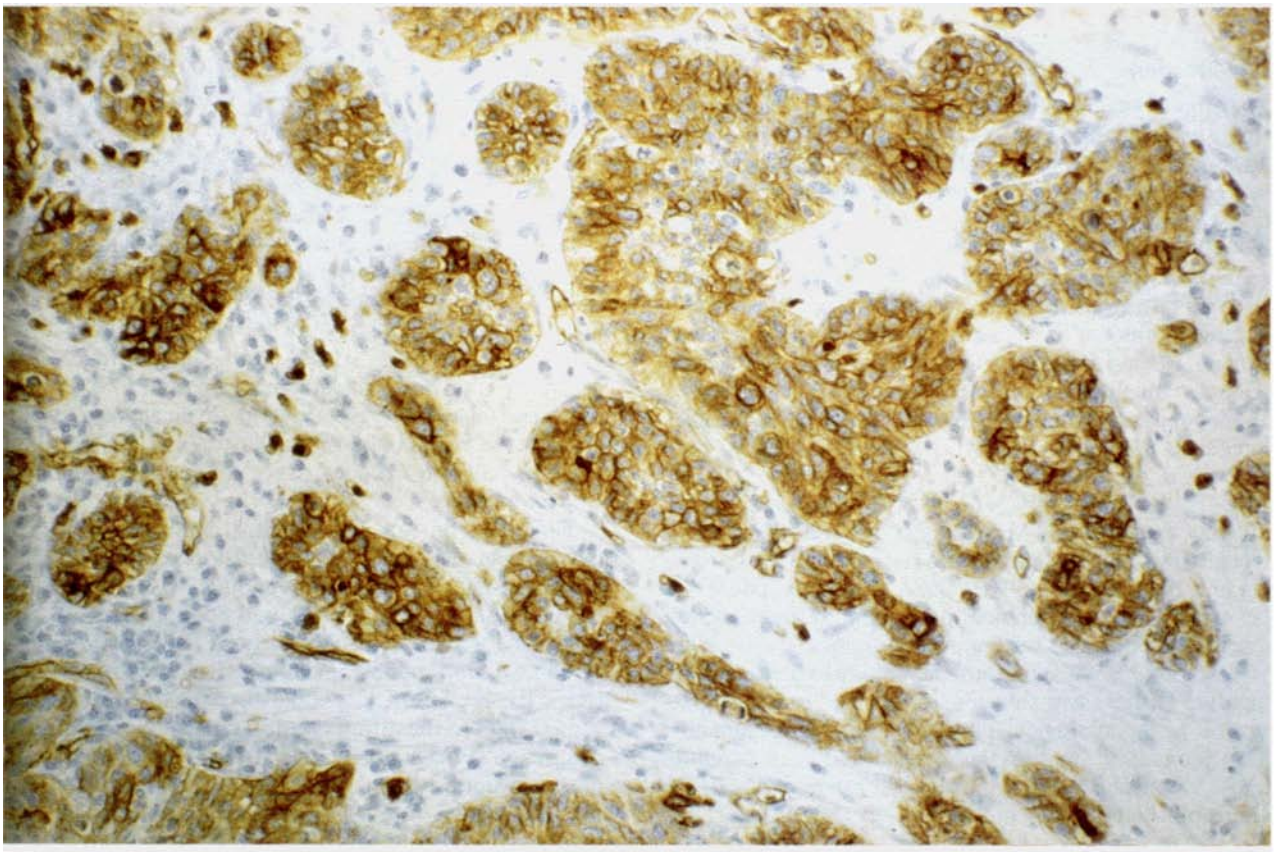

FIG. 1

Squamous cell carcinoma, base of tongue. Blood group immunostaining, showing strong postivity of all tumour cells.

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TABLE I
TABULATION OF THE TUMOUR CHARACTERISTICS TESTED ON H & E-STAINED SLIDES. FIGURES REPRESENT NUMBERS OF PATIENTS

	Tonsillar region	Base of tongue	Total
Cytonuclear pleomorphism*:			
mild	0	3	3
moderate	14	6	20
strong	2	4	6
Mitotic activity:			
low	6	4	10
moderate	4	4	8
high	6	5	11
Atypical mitoses:			
none	4	5	9
sporadic	8	7	15
few	4	1	5
many	0	0	0
Keratinization**:			
none	2	2	4
trace	5	4	9
moderate	4	3	7
marked	4	4	8
Inflammatory infiltrate:			
none	1	0	1
sparse	5	2	7
moderate	5	8	13
heavy	5	3	8
Stromal eosinophilia:			
absent	14	11	25
present	2	2	4
Tumour grade:			
undifferentiated	1	0	1
poorly differentiated	4	5	9
moderately differentiated	7	7	14
well differentiated	4	1	5

*p = 0.04 (between the subsites); ** one missing value in tonsillar carcinoma.

and five T4 tumours (UICC 1982 classification and staging system: UICC, 1982). Half of the tumours were ulcerating lesions, eight were predominantly infiltrative, three submucous, whereas the remainder was exophytic or mixed with red or white precancerous areas.

Histopathological studies

Formalin-fixed, paraffin-embedded sections of biopsy specimens were available in all instances. The slides were stained with haematoxylin and eosin, or according to routine immunohistochemical techniques. The following antibodies were used: polyclonal anti-collagen IV (Eurodiagnostics, 1:1000), a cocktail of monoclonal antibodies to blood group A, B and H antigen (Dakopatts, 1:25) (see Figure 1) and a monoclonal antibody recognizing keratin-10 (Ivanyi *et al.*, 1989a) (K_{10}, kindly provided by Dr D. Ivanyi, NKI, Amsterdam, 1:10) (see Figure 2).

The following morphological features were assessed semiquantitatively, using a standard scoring form: cytonuclear pleomorphism, mitotic activity, presence of atypical mitoses, keratinization, pattern of invasion, stromal eosinophilia, inflammatory infiltrate, tumour grade, expression of keratin-10, blood group antigens and collagen IV. All scores were reviewed by the first two authors (S.M.K. and W.J.M.) without prior knowledge of site and size of the primary lesion.

Statistical analysis

The morphological scores obtained on H & E and immunostained slides were tabulated and cross-tabulated. Each variable was also analysed with respect to the subsite. Of the macroscopic tumour characteristics, the T-category and macroscopic growth pattern (infiltrative, submucous, exophytic or ulcerating) were taken into account. Using the corrected Chi-square test p-values were calculated and considered significant when <0.05.

Results

The morphological features and the scores are listed in Table I. The tumour cell populations in the two subsites were similar with respect to mitotic activity, the presence of atypical mitoses, and keratinization. Cytonuclear pleomorphism was more marked in tonsillar carcinoma.

Compact invading strands of tumour were seen in all instances. Perineural tumour growth and angioinvasion were detected only occasionally. Some stromal eosinophilia was found in two cases in each site.

In the immunohistochemical tests, a number of cases did not yield a clear staining pattern, and were discarded from the statistical analysis. A difference by site was seen only in case of collagen IV, which was more often positive for tumours of the base of the tongue (Figure 3) than for those of the tonsillar region (Figure 4), (see Table 2).

Relationship between the scores obtained

All tested parameters were cross-tabulated (Table 3). A proportional increase in frequency of mitoses and of the presence of atypical mitoses was observed (p = 0.01). Mitotic activity was significantly higher in less differentiated tumours (p = 0.01). Low mitotic activity was associated with strong keratinization (p = 0.04). Atypical mitoses were more common in less keratinizing tumours (p = 0.03). More keratinization was seen in better differentiated tumours (p = 0.04). A higher K_{10} expression was found in the better differentiated tumours (p = 0.01). In tumours with no K_{10}-expression a trend towards higher

TABLE II
TABULATION OF THE TUMOUR CHARACTERISTICS TESTED ON MABS-STAINED SLIDES

	Tonsillar region	base of tongue	Total
K_{10}:			
++	4	1	5
focally positive	3	6	9
sporadic positive cells	1	0	1
no staining	4	6	10
missing	4	0	4
Collagen IV:			
continuous BM staining	2	6	8
focally strongly positive	1	2	3
focally weakly positive	7	2	9
no staining	1	1	2
missing	5	2	7
ABH:			
+++	5	5	10
positive	3	4	7
weakly positive	2	3	5
no staining	2	1	3
missing	4	0	4

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TABLE III
CROSS-TABULATION OF THE TESTED PARAMETERS. ONLY THE *P- VALUES* < 0.05 ARE PRESENTED

			Mitoses		
Atypical mitosis	0.01	Atypical mitoses			
Keratinization	0.4	0.03	keratinization		
Histological grade	0.01	NS	0.04	histological grade	
K_{10}	0.009	NS	NS	0.01	infl.
Collagen IV	NS	NS	NS	NS	0.03

NS = not significant.

mitotic activity was observed; focally strong K_{10} expression was associated with low mitotic activity ($p = 0.009$). Expression of collagen IV was higher in cases of more pronounced peritumoural inflammation ($p = 0.03$).

Cross-tabulation by macroscopic features of the tumours, i.e. the clinical aspect of lesions and the T-category did not reveal associations with any of the variables tested.

Discussion

In a number of previous papers on head and neck carcinomas, the morphological parameters tested in this study were demonstrated to correlate with each other (Jakobsson, 1973; Jakobsson *et al.*, 1973), with outcome after treatment (Broders, 1920; Bauer, 1974; Goldsmith *et al.*, 1987), or with survival rates (Loebe and Quade, 1982; Quade *et al.*, 1983; Quade, 1984; Quade and Loebe, 1984; Anneroth *et al.*, 1986). However, these features have not yet been standardized in a system of distinct categories of tumour differentiation, that would allow a reliable comparison of results from different studies. Several semi-quantitative grading systems employing these factors have been proposed (Jakobsson *et al.*, 1973; Loebe and Quade, 1982; Anneroth and Hansen, 1984), but none of them has become widely accepted. Tumour grading remains a relatively subjective matter, difficult to reproduce by other investigators (Broders, 1941; Cade and Lee, 1957; Stoddard, 1964; Arthur and Farr, 1972; Goldsmith *et al.*, 1987).

In analysing the errors occurring using Jakobsson's grading system (Jakobsson, 1973; Jakobsson *et al.*, 1973), Anneroth and Hansen (1984) identified three main sources of error: the absence of a clear definition of morphological parameters, possible interactions between the used variables, and technical shortcomings. We have attempted to standardize the categories and related scores in order to overcome the first error. We feel that a consistent use of a standardized checklist (possibly employ-

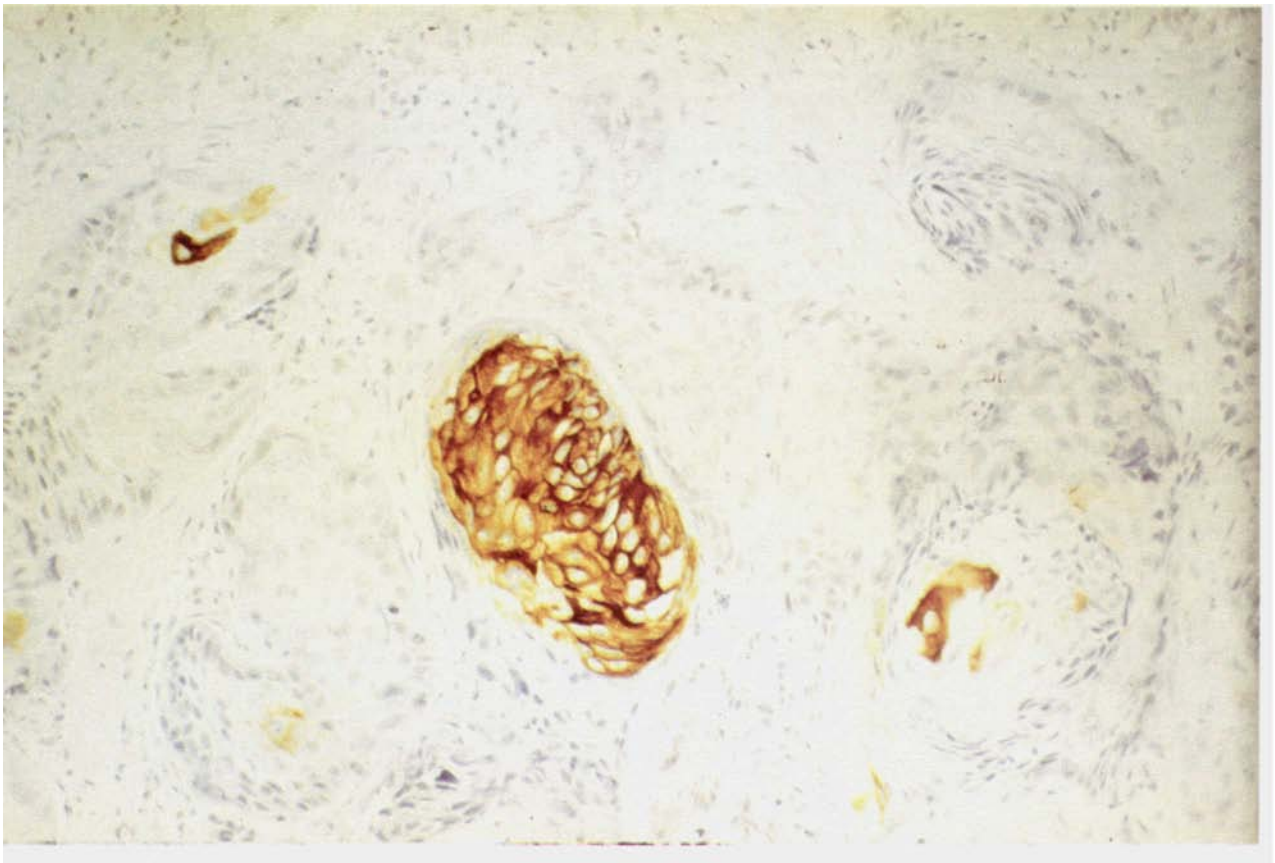

FIG. 2
Squamous cell carcinoma, base of tongue. K_{10} immunostaining, showing focal positivity in tumour cell nests.

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FIG. 3

Squamous cell carcinoma, base of tongue. Collagen IV immunostaining, showing an almost continuing basement membrane surrounding large nests of tumour cells.

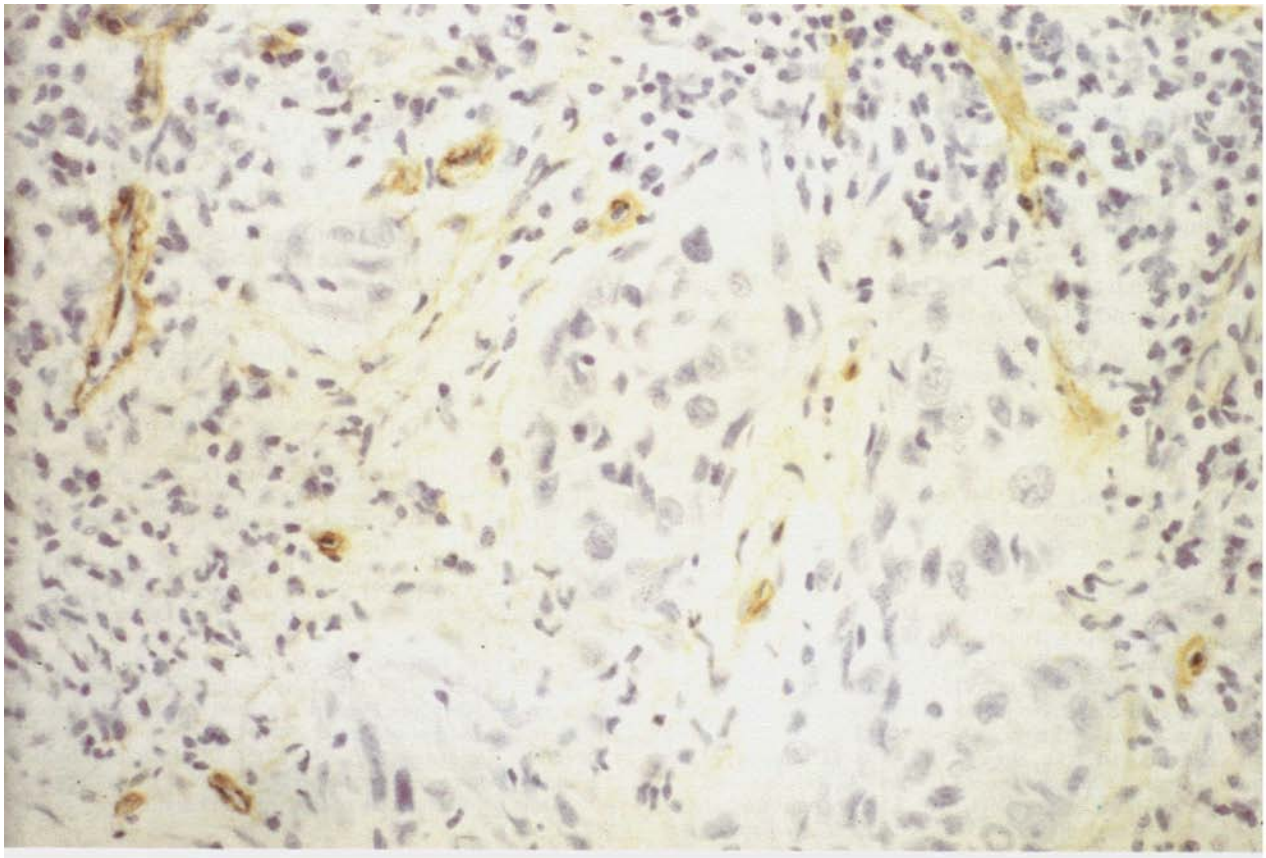

FIG. 4

Squamous cell carcinoma, tonsil. Collagen IV immunostaining, showing absence of basement membrane around tumour cell nests.

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ing additional parameters), may generate relevant data in larger series to support our clinical findings, despite the fact that in this limited number of patients insufficient evidence was obtained. The problem, of technical shortcomings however, remained unsolved. For example, the material sometimes precluded the assessment of some parameters associated with the tumour–host relationship: perineural growth and angioinvasion of tumour are more likely to be detected in surgical specimens than in biopsy material. Stromal eosinophilia, which was suggested to carry a favourable prognostic significance by Goldsmith *et al.* (1987), was present only occasionally in our material, and was never massive.

Cross-tabulation of the tested parameters revealed some expected outcomes in this study: correlation between a high mitotic activity and the presence of atypical mitoses, keratinization, and the tumour differentiation, respectively, as well as between K_{10} expression and tumour differentiation. Absence of correlation between keratinization and K_{10} expression was consistent with some observations in the early stages of vulvar squamous cell carcinoma, as reported by Ivanyi *et al.* (1989b). The authors suggested the irregular expression of K_{10} during the tumour development as a possible explanation for their results.

The relevance of the parameters tested has not yet been demonstrated specifically for the subsites of oropharyngeal carcinoma, possibly due to the relatively low incidence of these tumours. Therefore, we attempted to assess the morphological difference between tonsillar carcinomas and carcinomas of the base of the tongue. The only significant difference between the subsites, i.e. the degree of cytonuclear pleomorphism, does not appear to provide sufficient explanation for the observed different biological behaviour of these tumours. Some difference in expression of collagen IV was seen between the subsites, but this did not reach the level of significance in this series, possibly due to the small sample size and the high rate of nonevaluable slides (25 per cent). However, studies of the basal membrane might appear more promising in obtaining additional prognostic tumour characteristics. Other methods, such as flow cytometric DNA ploidy measurements, which have been shown to have prognostic value in T1 glottic carcinoma (Westerbeek *et al.*, 1993), should be evaluated with respect to substantiating the different biological aggressiveness of these two most frequent tumours in the oropharynx.

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