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Some histopathological and clinical correlations in oral squamous cell carcinoma

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ABSTRACT

Oral squamous cell carcinoma (SCC) is an important health problem that causes high mortality and morbidity. Correlations between some clinical and histopathological parameters were studied in 37 oral SCC. Some interesting aspects in oral SCC arising from precancerous lesions were found such as smaller size and a lower TNM stage at the moment of diagnosis. Histological and clinical differences were also found between tumors invading deep tissues by little groups of dissociated malignant cells and those invading by big masses of malignant cells. The possible significance of the intensity of peritumoral eosinophilic infiltrate was also studied.

Key words: Oral squamous cell carcinoma, Histopathological parameters, Clinical parameters

RÉSUMÉ

Le carcinome squameux de la cavité orale constitue un problème important de santé, qui est responsable d'une mortalité et d'une morbidité élevées. Nous avons étudié 37 carcinomes squameux de la cavité orale à travers un suivi clinique et une étude des corrélations entre les variables cliniques et histopathologiques. Nous avons relevé différents aspects intéressants en ce qui concerne les carcinomes squameux de la cavité orale qui procédaient de lésions précancéreuses comme leur petite dimention et le bas stade TNM au moment du diagnostic. Nous avons également trouvé des différences cliniques et histopathologiques entre les tumeurs qui envahissent les tissus adjecents en petits groupes et ceux qui le font en grandes masses de cellules malignes. Finalement, nous avons étudié la signification possible de l'intensité de l'infiltrat à eosinophiles peritumoral.

Mots Clef: Carcinome squameux de la cavité orale, variables cliniques, variables histopathologiques.

INTRODUCTION

Squamous cell carcinoma (SCC) is the most frequent tumor arising from the oral mucosa, and although it is an easy area for clinical exploration, at present the mortality rate of this process is very high. This fact is probably based on a delayed diagnosis, another very important result of which is the aggressiveness of the surgical treatment and consequent morbidity (Conte *et al.* 1989; Young *et al.* 1981). However, not all SCCs have a similar prognosis because there are some clinical and histopathological aspects affecting the evolution of oral cancer (Crissman *et al.* 1984).

The aim of this paper is to find some statistical correlations between the clinical and histopathological

aspects classically related to the biological behaviour of SCC and to study how these prognosis parameters are affected by those recently suggested; such as eosinophilic infiltrate sorrounding the tumor and the intensity of the inflammatory infiltrate adjacent to the lesion (Looi, 1987).

MATERIAL AND METHODS

Thirty seven patients with oral SCC were studied in the Oral Medicine Department of the University of Granada (Spain) between 1989 and 1991, and were revised in June, 1994.
70.3% (26 cases) were males and 29.7% (11 cases) were females, within an age range of 22 to 87 years (mean: 60 years, standard deviation: 14). A complete clinical history was performed and the patients were interrogated about some habits such as use of tobacco, alcohol consumption, oral hygiene, traumatic factors affecting the oral mucosa and the practitioner who detected the initial lesion (family doctor, dentist, dermatologist,...). Also the date of diagnosis, interval time between the first symptom reported by the patient and the diagnosis, clinical status at the moment of diagnosis, location, size, clinical appearance of the lesion and TNM stage were noted. Survival times in months both for first relapse (local or metastasis) or death (attributed to the tumor) were calculated up to june 1994.

Samples of all SCCs were formalin-fixed and paraffin-embedded. Sections were H & E stained. The histopathological study by an experienced pathologist included a diagnosis of the degree of differentiation (SCC well differentiated, moderatly well differentiated and poorly differentiated), type of tumoral growth (solid mass, cords, little groups or dissociated malignant cells), keratin production (absent, minimum, moderate, maximum), number of cells in mitosis, peritumoral eosinophilia, cytological atypia and the inflammatory infiltrate intensity. The quantifying methods' of parameters above noted are shown in table 4.

Descriptive statistics for the variables analyzed, along with the median survival time (both for death and relapse) were calculated. Association between clinical and histological variables which are cuantitative, dicotomic, or those which could be considered as ordinal were measured by means of spearman correlation coefficient. Analyses were performed by using BMDP (Dixon *et al.* 1990).

RESULTS

Tables 1, 2 and 3 shows clinical description of oral SCCs collected. The most relevant data is the high prevalence of tobacco and alcohol consumption, the low percentage of patients who practiced correct oral hygiene (table 1), the long time interval between the first symtom and diagnosis (mean 116 days, and in one case 547 days) and the low number of patients who were first diagnosed by a dentist (table 2).

TABLE 1: Description of oral cancer risk factors present in the studied tumors (n=37).
TABLEAU 1: Description des facteurs de risque du cancer oral dans les tumeurs qui ont fait l'objet de l'étude (n=37).

Variable	Distribution	
Tobacco habit (amount)[a]	no smoker	12 (34.3%)
	<20 cig/day	11 (31.4%)
	20-40 cig/day	10 (28.6%)
	>40 cig/day	2 (5.7%)
Tobacco habit (years)[a]	$\bar{x}$ = 22.9, SD = 19.1	
Alcohol consumption[b]	no drinker	12 (37.5%)
	small	2 (6.3%)
	moderated	13 (40.6%)
	hard-drinker	5 (15.6%)
Oral Hygiene[c]	No	27 (84.4%)
	Yes	5 (15.6%)
Traumatic factors[d]	No	20 (69.0%)
	Yes	9 (31.0%)
Oral sepsis[e]	No	8 (24.2%)
	Yes	25 (75.8%)

$\bar{x}$: arithmetic mean, SD: standard deviation.
a: 2 unknown, b: 5 unknown, c: 5 unknown; yes when the patient reported to brush his/her teeth at least once a day, d: 8 unknown; Yes when presence of traumatics prothesis or cutting borders of damaged teeth, e: 4 unknown; yes when mucosa inflamation or multiple caries were detected in the mouth.

From table 2 the preference of patients to consult their family doctor as the first option could be deduced.

A great percentage of the tumors (68.6%) were ulcerated lesions. 16.2% were found to arise from precancerous lesions (leukoplakia and lichen planus). 64.8% of the neoplasms were greater than 4 cm in diameter or had invaded deep tissues. A very high proportion (75.6%) of the patients were in TNM stage III or IV (table 3). Further results not shown in table 3 indicate that none patients presented metastases (M0) when the clinical and histological variables were measured. Median survival times for relapse was 42.5 months, and 45 months for death.

TABLE 2: Results in relation to the initial diagnosis of the oral cancer (n=37).
TABLEAU 2: Résultats en fonction du diagnostic initial du cancer oral (n=37).

Variable	Distribution	
Elapsed time (days) between first sympton and diagnosis[a]	$\bar{x}$=116, SD=128	
Practitioner by whom patient was referred	Family doctor	19 (51.4%)
	Dentist	3 (8.1%)
	Dermatologist	7 (18.9%)
	Family doctor & dentist	2 (5.4%)
	by himself	6 (16.2%)
Practitioner that visited the patient and did not suspected the lesion	Family doctor	10 (27.0%)
	Dentist	2 (5.4%)
	Dermatologist	7 (18.9%)
	Family doctor & dentist	4 (10.8%)
	None	14 (37.8%)

$\bar{x}$: arithmetic mean, SD: standard deviation.
a: 3 unknown.

TABLE 3: Clinical variables of the studied tumors (n=37)
TABLEAU 3: Résultats cliniques de l'étude (n=37).

Variable	Distribution	
Tumoral location	Tongue base	3 (8.1%)
	Lateral margin of the tongue	6 (16.2%)
	Floor of the mouth	5 (13.5%)
	Gingiva	9 (24.3%)
	Buccal mucosa	14 (37.8%)
Clinical appearance[a]	Exophitic	5 (14.3%)
	Endophitic	3 (8.6%)
	Ulcerated	24 (68.6%)
	Verrucous	3 (8.6%)
Tumors arise from precancerous lesion	No	31 (83.8%)
	Yes	6 (16.2%)
Tumoral size	<2 cm.	4 (10.8%)
	2-4 cm.	9 (24.3%)
	>4 cm.	8 (21.6%)
	Invasion of deep tissues	16 (43.2%)
Affect on cervical nodes at diagnosis	N0	22 (59.5%)
	N1	11 (29.7%)
	N2a	1 (2.7%)
	N2b	2 (5.4%)
	N2c	1 (2.7%)
Stage (TNM)	I	4 (10.4%)
	II	5 (13.8%)
	III	11 (29.7%)
	IV	17 (45.9%)

a: 2 unknown.

The histopathological results are shown in table 4. The largest group of tumors were moderately well differentiated (64.9%) and in 67.6% the tumoral growth was in the form of a solid mass. A moderate to abundant keratin production was observed in the majority of the lesions (91.8%).

A low number of mitotic figures were found in 62.2% of the cases and in a high percentage of the lesions a little eosinophilic inflitrate surrounding the tumor was observed (67.6%).

TABLE 4: Histopathological description of the studied tumors (n=37).
TABLEAU 4: Résultats histopathologiques de l'étude (n=37).

Variable	Distribution	
Histopathologycal diagnosis[a]	Well differenciated	10 (27.0%)
	Moderately well differenciated	24 (64.9%)
	Poorly differenciated	1 (2.7%)
	Spindle cells carcinoma	2 (5.4%)
Tumoral growth[a]	Solid	25 (67.6%)
	Cords	3 (8.1%)
	Little groups of tumoral cells	7 (18.9%)
	Dissociated cells	2 (5.4%)
Keratin production[a]	Absent	2 (5.4%)
	Minimum	1 (2.7%)
	Moderated	18 (48.6%)
	Maximum	16 (43.2%)
N° of mitoses	0-1/8 fields/40x	23 (62.2%)
	1-2/8 fields/40x	6 (16.2%)
	2-5/8 fields/40x	6 (16.2%)
	<5/8 fields/40x	2 (5.4%)
	>5/8 fields/40x	
Peritumoral eosinophilia	5-15/8 fields/40x	25 (67.6%)
	16-25/8 fields/40x	7 (18.9%)
	26-50/8 fields/40x	2 (5.4%)
	>50/8 fields/40x	1 (2.7%)
		2 (5.4%)
Cytological abnormality[a]	Grade I	8 (21.6%)
	Grade II	25 (67.6%)
	Grade III	4 (10.8%)
Inflammatory infiltrate intensity[a,b]	Grade I	11 (30.6%)
	Grade II	14 (38.9%)
	Grade III	11 (30.6%)

a: the quantifying of this parameters was based in the personal experience of the oral pathologist, b: 1 unknown.

Correlations for those variables which shown significant associations are presented in table 5.

DISCUSSION

Oral SCC is an important health problem more frequently affecting males (Moore *et al.* 1987). Some aetiological factors related to tumoral development are known, tobacco and alcohol use being accepted as the most important ones today (Conte *et al.* 1989), although other biological factors such as different Human Papilloma virus types, have recently been related (González-Moles *et al.* 1994). The current authors found a significant statistical correlation between the intensity of these habits and some clinical

TABLE 5: Spearman correlation coefficients between clinical and histological parameters in the 37 patients.
TABLEAU 5: Coefficient de corrélation de Spearman entre les paramètres cliniques et histopathologiques de l'étude chez 37 patients.

	Tobacco habit (amount)	Tobacco habit (years)	Alcohol consumption	Presence of precancerous lesion	Cervical nodes	Tumoral growth	Peritumoral eosinophilia
Tumoral size	0.34*	0.35*	0.52**	−0.34*	0.18	0.04	0.16
Cervical nodes	0.24	0.18	0.43*	−0.21	—	0.39*	0.22
Stage (TNM)	0.31	0.37*	0.52**	−0.34*	0.37*	0.01	0.09
Tumoral growth	0.28	0.11	0.30	−0.21	0.39*	—	0.29
Keratin production	−0.18	−0.20	−0.22	0.02	−0.25	−0.54**	0.05
Cytological abnormality	0.07	0.02	0.14	−0.31	0.42**	0.27	0.33*

* $p > 0.05$, ** p0.01. Variable codes are described in tables 1 to 4.

and histopathological prognosis parameters of the lesions, such as bigger tumoral size, invasion of cervical nodes, superior TNM stage at diagnosis. In this way, both the amount and the time of tobacco consumption, show a similar association with the tumoral size and TNM stage. The authors consider that hard smokers and drinkers are probably careless with their oral health and that there may be a delay between the onset of cancer symptoms and the first medical examination. However, a more aggressive effect on the cellular genetic material could also be feasible when tobacco and alcohol consumption is very high.

Sometimes, oral SCC appear following a precancerous lesion (leukoplakia, lichen planus...). This fact occurred in 16.2% of the cases in the present study and some differences were observed in those cases. Tumors arising from precancerous lesions were smaller in size and their TNM stage was also lower (table 5). In addition, the number of mitotic figures and the degree of cellular atypia were less prominent than in oral SCCs not preceded by precancerous lesions (dates close to statistical significance, $p = 0.06$). It could be that patients affected by precancerous lesions had been periodically examined and that the malignant transformation could be detected at a lower tumoral size and TNM stage. However, some parameters reflect lower histological aggressiveness in oral SCCs arising from precancerous lesions and again leading to a consistently smaller tumoral size and lower TNM stage at the moment of diagnosis.

A poor evolutionary prognosis is generaly accepted in oral SCCs invading deep tissues by means of little groups of malignant cells or dissociated malignant cells (Martin *et al.* 1980; McGravran *et al.* 1961; Yamamoto *et al.* 1983). In agreement with Hibbert *et al.* (1983) and Ildstad *et al.* (1989), the present study shows that cervical node affectation was statistically associated with an aggressive form of tumoral invasion and with a high degree of cytological abnormality. Lower keratin production was also found when an agressiveness form of invasion was present. Regarding the final observation of this paper, a controversy about the significance of the inflammatory infiltrate in human cancer has recently been established. Whereas, for a long time, a greater tumoral inflammatory infiltrate was considered to be a good evolutionary prognostic factor, some investigators (Prenh and Prenh, 1987) now postulate that specific tumoral immune reaction could in the end be an important help to cancer development, perhaps by stimulation of tumoral growth related to the production of growth factors in inflammatory cells (Gómez-Morales *et al.* 1991). In the present paper no clinical or histological differences were found in the intensity of the peritumoral inflammatory infiltrate between the oral SCCs studied and no consistant relationship was found with other prognostic parameters.

Similar controversy exists over the prognostic significance of peritumoral eosinophilia as a result of discordant interpretation of its functions by different authors. Recently, tumor associated eosinophilia has been related to a good prognosis of the lesion by its cytotoxic capacity (Looi, 1987) and an elevated number of peritumoral eosinophilic cells associated with an increase in survival time (Lowe and Fletcher, 1984; Milian *et al.* 1993). Also, McKee *et al.* (1983) found a very high number of eosinophilic cells sorrounding the lesion in tumors with poor keratin production and moderately good differentiation. The

current authors' results show a statistically association between the increase in the number of eosinophillic peritumoral cells and elevated cytological abnormality. Although seemingly the results contradict other investigations, it could be that a more tumoral cellular atypia may generate a larger eosinophilic peritumoral defensive response. Conversely some authors (Pastrñak and Jansa, 1984; Bostrom and Hart, 1981) have found an increase in the secretion of tumoral growth factors by eosinophilic cells which is in disagreement with that expounded above.

Hence, and as a result of these diverse opinions in relation to distinct aspect related to the prognosis of oral SCC, in the opinion of the authors more extensive studies are necessary in order to clear up these controversial aspects.

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