

Cell Cannibalism in Oral Precancerous Lesions and Squamous Cell Carcinoma

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Abstract

Introduction:

Cellular cannibalism is defined as a process of non-apoptotic cell death. This phenomenon has been indicated to be associated with aggressiveness, anaplasia, invasiveness, and metastatic potential of various malignancies. The Aim of this study is the evaluation of cell cannibalism in oral dysplastic lesions and oral cancer.

Materials and Methods:

A total of 31 cases of squamous cell carcinoma (SCC), 30 epithelial dysplasia, and 36 hyperkeratosis (HK) were enrolled in this Cross-sectional study. All hematoxylin and eosin tissue sections were examined in 10 high-power fields for tumor cell cannibalism. Data were analyzed using the Kruskal-Wallis and Fisher's exact test.

Results:

Cell cannibalism was found in all cases of SCC, 58.3% of dysplastic lesions, and 3.7% of HK cases. The mean number of cells with cannibalism was 19.48 ± 4.94 in SCC patients, 1.03 ± 1.25 in dysplastic lesions, and 0.03 ± 0.18 in HK with a significant difference ($P < 0.001$). High grades dysplastic and cancerous lesions exhibited more cannibalistic cells ($P = 0.01$, $P = 0.27$, respectively).

Conclusions:

In addition to oral SCC, cell cannibalism was found in oral epithelial dysplasia; which was significantly more in SCC. This phenomenon was in association with grades of differentiation and might be considered a potential criterion for malignant transformation and high-grade lesions.

Keywords: Cannibalism; Carcinoma, Squamous Cell; Cytophagocytosis, Mouth Neoplasms.

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Introduction

Oral cancer remains a major cause of morbidity and mortality in patients with head and neck cancer and the eleventh most common cancer globally (1). Since at the time of diagnosis, most of these cancers progress to an advanced stage, the 5-year survival rate is low (2). It is important to note that the survival rate with early diagnosis and therefore early treatment can be raised to 80% (3). Oral squamous cell carcinoma (OSCC) consists of more than 90% of oral malignant lesion (4,5). Precancerous lesions, which are called oral potentially malignant disorders, are a heterogeneous group of oral mucosal lesions can transform to the oral cancer (6). Early detection and treatment of these lesions can improve the survival rate. Abnormal or atypical epithelial proliferation leading to poor epithelial layer differentiation and maturation disturbance can be found in histological assessments (7). Among several classification systems for dysplasia, the WHO classification (mild, moderate, and severe) is the major one applied by pathologists for diagnosis (8). In addition, the presence of oral epithelial dysplasia increases the risk of the progression of the lesion to the malignancy (9). Cellular cannibalism (also known as cell-in-cell formation, in-cell invasion, or cell-in-cell phenomenon) is defined as a process of non-apoptotic cell death in which the slightly smaller cell is surrounded by a larger one within its cytoplasm for its survival; this is the histopathologic characteristic of aggressive malignancies leading to degradation of the swallowed cell by lysosomal enzymes of larger cell (10). This histological feature has been frequently reported in malignant lesions; however, it has not been well recognized in precancerous lesions. Steinhaus described the earliest cannibalism in tumor cells at a cellular level (11). In this process, the living cell is engulfed, resulting in the unusual appearance of whole cells within large vacuoles; this process finally leads to its death. In case of limited nutrients, malignant cells increase feeding through the cannibalism mechanism, and as a result, they increase their survival and progression (12). This characteristic distinguishes cannibalism from other types of cell engulfment, such as phagocytosis, autophagy and entosis (13). This phenomenon is associated with the degree of aggressiveness, anaplasia, invasiveness, and metastatic potential

of various malignancies (14,15). In previous studies, cannibalism cells were assessed in different cancers, such as OSCC, salivary duct carcinoma, and malignant melanoma (14). Presence of cannibalism in malignant lesions has been frequently studied, and some researchers have introduced it as a sign of cancer development and progression; however, there is not sufficient information about cannibalism in patients with precancerous lesions. In this study, we intend to investigate if cannibalism in dysplastic lesions can be considered a criterion for the progression of lesions to malignancy.

Materials and Methods

In this cross-sectional study, histopathologic slides related to patients with the final diagnosis of OSCC and dysplastic lesions, who referred to the Pathology Department of the School of Dentistry of Shiraz University of Medical Sciences from 2005 to 2020, were studied.

Slides with cases that had adequate epithelial tissues and a definitive diagnosis were included and were examined for the presence of cell cannibalism. Slides with inadequate epithelial tissues, without a definitive diagnosis, and recurrent squamous cell carcinoma (SCC) were excluded. Thirty cases of epithelial dysplasia, 31 cases of OSCC, and 36 cases of hyperkeratosis (HK) were enrolled as the control group. Baseline data of all cases, including patients' gender and age, as well as histopathologic grade of dysplastic and cancerous lesions, were noted.

5 µm hematoxylin and eosin (H & E) stained sections were examined in 10 high power fields (Hpf) with ×400 magnification, to find tumor cell cannibalism (TCC). Cannibalistic cells were large tumor cells with circular nuclei, which enclosed or surrounded a smaller tumor cell. Overlapping tumor cells, dyskeratotic cells, vacuolated cells, and tumor cells surrounding inflammatory cells were excluded. The whole slide was scanned, and TCCs were counted in 10 fields with the maximum density of this phenomenon recorded as TCC/10Hpf (16). Then, based on TCC/10 Hpf, TCCs were classified into grade 1: <5 cannibalistic cells, grade 2: 6-15 cells, and grade 3: >16 cells (17). This study was approved by the Institutional Review Board (IRB) of Shiraz University of Medical Sciences and the Ethics Committee (IR.SUMS.DENTAL.REC.1400.013).

Statistical Analysis

Data were analyzed using the SPSS software version 25. Kruskal-Wallis and Fisher's exact tests were used to compare the variables. P-value <0.05 was considered statistically significant.

Results

A total of 97 cases were evaluated, including 36 cases of HK, 30 cases of dysplastic lesion, and 31 cases of SCC. The patients' mean age was 54.4±14.7, and 55.7% of them were female (Table 1).

Table 1: Clinical data of all study groups

Group(N)	Grade(N)	M: F	Age (Mean± SD)	P-value
SCC (31)	Poor (4)	3:1	57.0 ±12.1	-----
	Moderate (9)	4:5	47.3± 13.3	
	Well (18)	11:7	62.9± 13.0	
Subtotal		18:13	57.6± 14.4	
Dysplasia (36)	Mild (10)	2:8	55.8± 19.4	
	Moderate (14)	2:12	59.9± 13.6	
	Sever (12)	5:7	56.4± 14.6	
Subtotal		9:27	57.6± 15.4	
Hyperkeratosis (30)	---	16:14	47.3± 12.0	
Total		43:54	54.4± 14.7	

Cell cannibalism was observed in 100% of SCC, 58.3% of dysplasia, and 3.7% of HK patients. According to the Chi-square test, this difference was significant (P<0.001) (Table 2).

Histopathologic micrographs of cannibalistic cells with semilunar nucleus in cases of SCC and dysplasia are shown in figure 1 and 2.

Table 2: Cell cannibalism status in all groups

Group(N)	Grade(N)	Cell cannibalism				P-value
		Negative	Positive	Mean± SD	Median	
SCC (31)	Poor (4)	0 (0)	4 (100)	22.25± 6.13	21.5	0.27*
	Moderate (9)	0 (0)	9 (100)	20.56± 6.37	19	
	Well (18)	0 (0)	18 (100)	18.33± 3.68	18	
Subtotal		0 (0)	31 (100)	19.48± 4.94		
Dysplasia (36)	Mild (10)	7 (70.0)	3 (30.0)	0.40± 0.70	0	
	Moderate (14)	6 (42.9)	8 (57.1)	0.71± 0.73	1	
	Sever (12)	2 (16.7)	10 (83.3)	1.92± 1.62	2	
Subtotal		15 (41.7)	21 (58.3)	1.03± 1.25		
HK (30)	-----	29 (96.3)	1 (3.7)	0.03± 0.18	0	
Total	-----	44(45.4)	53 (54.6)	6.62± 9.32	1	

SCC: squamous cell carcinoma, HK: hyperkeratosis, *ANOVA test

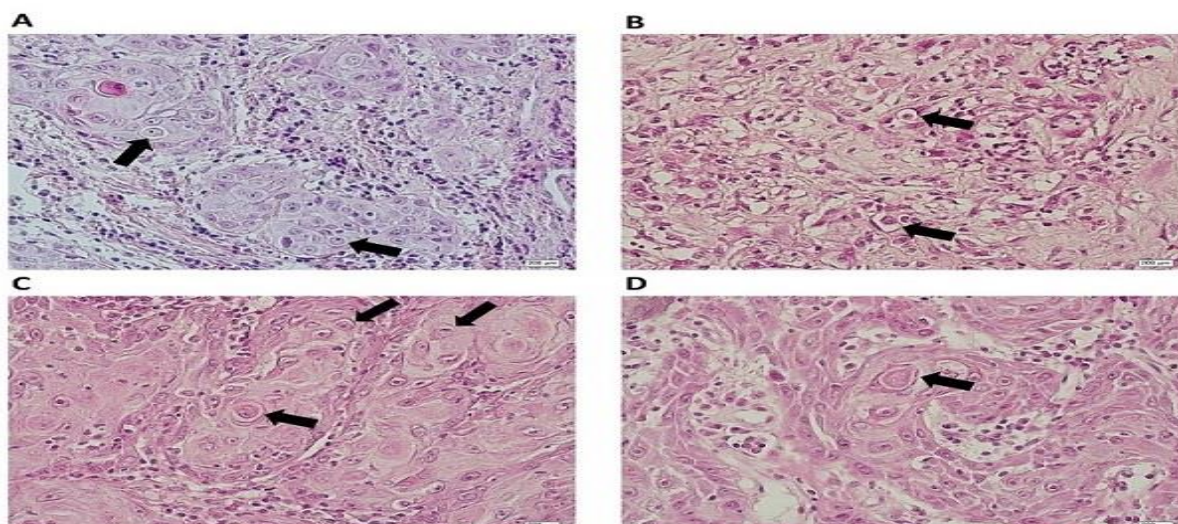


Fig 1: Cannibalistic cells with semilunar nucleus (black arrows) in cases of squamous cell carcinoma. Larger cells engulfing smaller cells. (Hematoxylin and eosin staining, A and B×400, C and D×200).

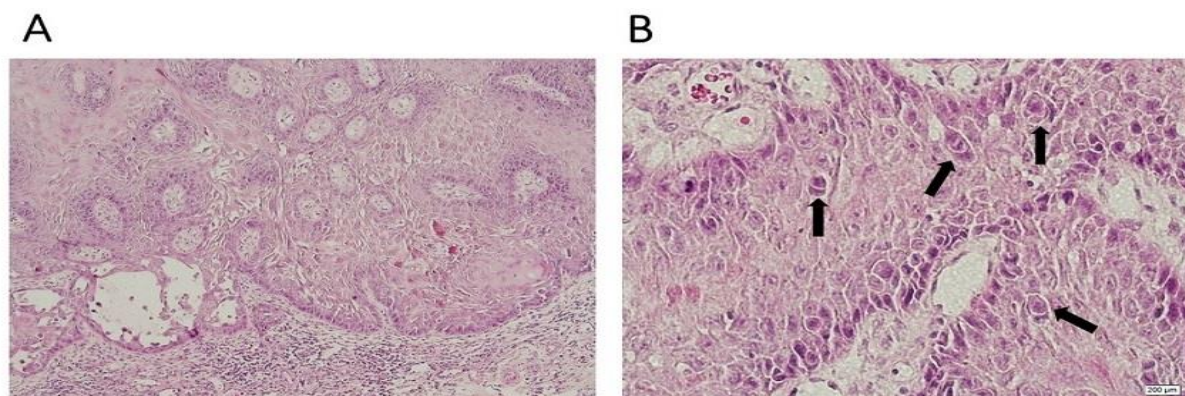


Fig 2: Cannibalistic cells with semilunar nucleus (black arrow) in cases of epithelial dysplasia. (Hematoxylin and eosin staining, A×200, B×400).

The mean number of cells with cannibalism was 19.48 ± 4.94 in SCC, 1.03 ± 1.25 in dysplasia, and 0.03 ± 0.18 in HK patients. ANOVA test showed the significant difference ($P < 0.001$). The mean \pm SD of cells with cannibalism was 22.25 ± 6.13 in

poorly differentiated SCC, which was decreased to 20.56 ± 6.37 and 18.33 ± 3.68 in moderately differentiated and well differentiated cases, respectively, without any statistically significant difference ($P = 0.27$) by the ANOVA test (Fig3).

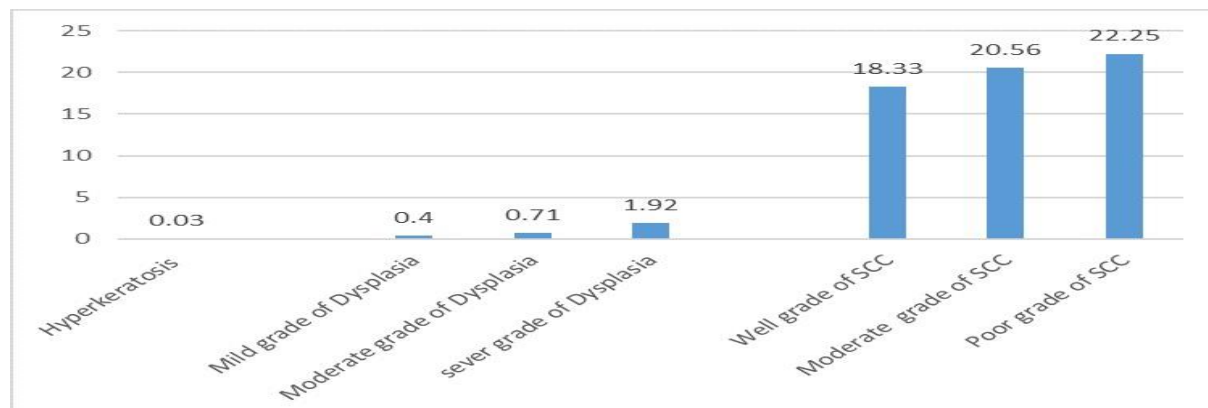


Fig 3: Mean number of tumor cell cannibalism (TCC/10Hpf) in each histopathologic diagnosis

Table 2 shows the mean± SD of cells with cannibalism in different grades of dysplasia. Severe dysplasia revealed a significantly higher TCC compared to mild and moderate grades using the ANOVA test (P=0.01). As Table 3 illustrates, most of the SCC patients showed the grade 3 of cell cannibalism with no significant

difference among different grades of SCC (P=0.65). Most of the patients with dysplasia presented the grade 1 cell cannibalism, and the Fisher's exact test demonstrated no significant association between the grade of lesion and the grade cell cannibalism (P=0.06). One patient with HK revealed the grade 1 cell cannibalism.

Table 3: Cell cannibalism grades in all groups

Type (N)	Grade(N)	Cell cannibalism grade N (%)				P-value*
		No cannibalism	Grade 1	Grade 2	Grade3	
SCC (31)	Poor (4)	0 (0)	0 (0)	0 (0)	4 (100)	0.65
	Moderate (9)	0 (0)	0 (0)	1 (11.1)	8 (88.9)	
	Well (18)	0 (0)	0 (0)	4 (22.2)	14 (77.8)	
Dysplasia (36)	Mild (10)	7 (70.0)	3 (30.0)	0 (0)	0 (0)	0.06
	Moderate (14)	6 (42.9)	8 (57.1)	0 (0)	0 (0)	
	Sever (12)	2 (16.7)	9 (75.0)	1 (8.3)	0 (0)	
HK (30)	-----	29 (96.3)	1 (3.7)	0 (0)	0 (0)	----
Total (97)		42	35	6	26	

SCC: squamous cell carcinoma, HK: hyperkeratosis, *Fishers' exact test

Discussion

TCC, also known as anthropophagy, is defined as a large cell engulfing a smaller one within its cytoplasm. Although this phenomenon is not new in the field of pathology, its significance is not still completely recognized. This phenomenon appears in various human tumors, and is regarded as an exclusive property of malignancy. It is related to the histopathologic grade, invasiveness, aggressiveness and metastatic potential of several malignancies (14, 15). Most of previous studies were focused almost on malignant tumors like SCC, they paid less attention to premalignant lesions in term of cell cannibalism. In the present study, we investigated TCC in oral HK, dysplastic lesions, SCC, and its association with histopathologic grade. Percentage of TCC positive cases and the mean cannibalism cells were more in SCC, dysplasia and HK, respectively. Furthermore, the mean number of CC increased with increasing SCC or dysplasia grade, which was statistically significant in

dysplastic lesions. Cell cannibalism was observed in 100% of SCC patients with the mean number of 19.48 cells in 10 Hpf, which increased with gaining the SCC grade in our study. Moreover, most of them exhibited the grade 3 cell cannibalism. The percentage of positive TCC cases of SCC in previous studies was slightly different. In one study conducted by Kinoshita et al., 60% of patients with poorly differentiated SCC of the breast exhibited cellular cannibalism (18). The result of this study is in line with another study conducted by Jose et al. on 20 cases of neck dissection of OSCC, which indicated that all cases with different histopathologic grades showed TCC (19). Jain et al. reported a mean of 10.88 and 7.57 TCC in moderately and well-differentiated metastatic SCC, respectively; which were slightly less than our results (17). Sarode et al. assessed neutrophil-tumor cell cannibalism (NTCC) in 500 cases of OSCC (20). They found that classical features of cannibalism were detected only in seven (1.4%) cases. All of these cases were poorly differentiated and

accompanied by cervical lymph node metastasis. They concluded that NTCC in cases with OSCC could be considered a predictor of biological behavior and a good prognostic marker. Overall, most of previous studies were in line with our results and showed that TCC was found in a notable percentage of SCC cases.

The findings showed more TCC in high grades tumors. Several studies confirmed the association of TCC with OSCC grades (17, 21). Jose et al. (22) evaluated 20 cases and found that an advanced grade (grade 3) of TCC was associated with lymph node metastasis and proposed that TCC could be considered one of the crucial parameters to predict the aggressive nature of OSCC. Additionally, some researchers revealed the association of TCC with the metastasis of oral cancer and overall survival and prognosis (17). Some previous studies explained that cannibalism could be regarded as a feeding activity of malignant tumors for survivals (23). Lugini et al. found that living T cells, which were programmed to kill metastatic cells, were engulfed by human metastatic melanoma cells. This occurrence can be considered a new mechanism for tumor cell to escape from the immune system. Furthermore, they stated that in an unfavorable microenvironment, malignant tumor cells applied cannibalism for their feeding activity, particularly under starvation and low nutrient supply conditions to increase their survival and progression. This mechanism remarkably increased metastatic melanoma cell survival (14). TCC was also reported in other human cancers. One study conducted by Kinoshita et al. aimed to determine the diagnostic cytological features of the poorly differentiated SCC of the breast compared to other histopathologic types of breast carcinomas (18). They found that cannibalism was significantly frequent in SCC and reported it to be one of the useful cytological features for the diagnosis of the SCC of the breast. They also reported the association of NTCC with an aggressive, metastatic, and high grade salivary duct carcinoma of the parotid gland (24). Overall, it can be concluded that cannibalistic cells are associated with progression to malignancy and are a helpful indicator for cancer diagnosis. Owing to the mentioned characteristics of cannibalistic cells, many researchers have suggested that in the routine histopathology assessment of cancers, this

phenomenon should also be used to predict the behavior of cancers. In one review study, Jane recommended screening each cancer specimen in terms of TCC to validate its role as a morphological predictor (15,17).

The present study revealed that 58.3% of the patients with epithelial dysplasia showed CC with the mean number of 1.03 cells, which increased along with increasing the grade of dysplasia. Moreover, most of the patients with dysplasia showed the grade 1 CC. There are few studies on cannibalism in dysplastic lesions. Demir et al. evaluated 75 patients with confirmed severe dysplasia based on urinary bladder washing cytology (25). They found that in 65% of cases, cannibalism was detected, which is slightly more than our result. Moreover, Kim et al. assessed CC in dysplastic gastric lesions (26). They found that 14% of cases with low-grade dysplasia and 54% with high-grade dysplasia exhibited CC. These results are consistent with our findings. However, some researchers like Domingo-Claros et al. proposed that CC was not the characteristic of dysplastic lesions found in malignant cases (12). Additionally, another study revealed that cannibalistic cells were detected only in invasive SCC, not in dysplasia or carcinoma in situ (27). Overall, since there are not many studies on the role of cannibalism in dysplastic lesions, particularly in oral lesions, it appears that more studies should evaluate the significance of CC in precancerous lesions. Some hypotheses have investigated why CC occurs in precancerous conditions (28). First, in the cannibalism phenomenon, the cytokinesis of swallowing cells is disrupted by swallowed cells, leading to development of aneuploidy that causes tumor growth (29). Second, in the lack of sufficient nutrient supply for the high proliferation rate in a precancerous lesion, CC could indicate increased proliferation (29). Finally, the acidity of the microenvironments of precancerous lesion also contributes to CC, since cannibalistic cells, unlike normal cells, are resistant to the acidity of microenvironments and can survive (22).

In the present study, at least in one case of HK, cell in cell phenomenon was detected. Owing to the small size of cells in the basal layer of HK, this finding should be confirmed by an immunohistochemical study. Further research is also required to confirm this novel finding. The CC in oral lichen planus (OLP), which has

histological similarity with HK, was mentioned in the literature in a limited way. OLP is an immune-mediated, chronic inflammatory disorder, which is considered a premalignant condition, with an increased risk of malignant transformation (28). One study hypothesized that the risk of malignant transformation in OLP increases in cases of cannibalism observations. Thakur et al. evaluated surface epithelial cells in OLP by a scanning electron microscope (30). They found that apparent cell cannibalism was not observed in all 15 cases.

In the present study, the rate of CC was increased with the progression of malignant changes from hyperkeratosis to cancer. Furthermore, the higher grades of SCC and dysplasia showed more CC compared to well-differentiated cases. It has been revealed that CC could indicate the malignant changes and its severity. Similarly, some studies also demonstrated that the cannibalism phenomenon was associated with malignant transformation and the grade of differentiation (21,22).

One limitation of the present study was the low number of high-grade lesions for more accurate results. It is recommended that IHC markers related to cannibalism, such as CD68 and caveolin, as well as its association with clinical parameters, be investigated.

Conclusion

In conclusion, our data indicated CC in both epithelial dysplasia and SCC. Moreover, CC was associated with high grades of dysplasia and SCC, and the number of cannibalistic cells increased as the disease progressed from HK to high grade SCC.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Shiraz University of Medical Sciences (2021/IR.SUMS.DENTAL.REC.1400.013).

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Conflict of interest

None.

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