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Clinicopathologic features, tumor staging, and intratumoral inflammation in canine oral non-tonsillar squamous cell carcinomas

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Abstract
Oral cancers, such as squamous cell carcinomas, constitute important diseases in veterinary patients, as they are frequently observed in pets. Their usually aggressive behavior makes it critical to characterize the clinicopathologic features that can provide useful data for decision-making. Recently, the importance of inflammatory cell infiltration in different tumor types has been highlighted due to its association with clinical findings and outcomes. Thus, this study aimed to evaluate clinicopathologic features in 62 cases of canine oral non-tonsillar squamous cell carcinomas, as well as to investigate tumor infiltration by inflammatory cells and its relation to clinical staging. Statistically significant results were observed when comparing neutrophil infiltration in stage 2 patients and animals presenting higher stages (3 and 4). Patients in stages 3 and 4 revealed lower neutrophil infiltration than stage 2 dogs. Histological grading showed differences in mitotic count between less differentiated and well/moderately differentiated neoplasms. Such features—especially those related to neutrophil infiltration and tumor staging—are relevant for the comprehension of non-tonsillar tumors, consequently aiding in decision-making in cases of canine oral squamous cell carcinoma in dogs.

Keywords: Oncology, cancer, tumor infiltration, neutrophils, dog.

Introduction

Canine squamous cell carcinomas are tumors considered to be frequently aggressive, especially when compared to their cutaneous counterparts (24). Despite advances in veterinary medicine and the consequent increase in the life expectancy of dogs, carcinogenic mechanisms associated with oral tumors may have environmental influences similar to those in humans (5). This feature may cause differences in these tumors among dog populations in each country, making research in this specific area very important to provide more information about the disease's biological behavior.

Canine oral squamous cell carcinomas can be divided into tonsillar and non-tonsillar types due to variations in their biological behavior. Tonsillar carcinomas usually have a higher metastatic potential at diagnosis; however, they are less frequently observed than non-tonsillar tumors in dogs (8, 22, 38).

The TNM system can be used as a prognostic indicator for canine patients with oral squamous cell carcinoma. However, since it is not always accurate, it may be necessary to associate results with other ancillary methods and histopathologic features, such as histologic grading, to obtain better outcomes (22). This is extremely important because failure in early detection, silent development, tumor size, and location can limit treatment options (23). Consequently, research involving information that can provide an accurate diagnosis and determination of tumor characteristics associated with decision-making (i.e., histopathologic and molecular data) is necessary (20).

In humans, evidence points to a relationship between inflammation and various aspects of tumor evolution and progression in several cancer types (10, 14, 17, 29, 42

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including oral squamous cell carcinomas (13). Among inflammatory cells, tumor-associated neutrophils (TAN) have been highlighted due to their potential anti- and protumoral functions (20, 32).

Since canine oral squamous cell carcinomas (OSSC) usually present a poor prognosis, the characterization of new features that can be related to histopathologic analysis and staging—consequently aiding in decision-making—is encouraged. Thus, the aim of this study was to assess clinicopathologic parameters and tumor staging, with particular focus on intratumoral inflammation.

Materials and Methods

Case selection and sample collection

For this retrospective study, 62 non-consecutive cases of canine oral non-tonsillar squamous cell carcinoma diagnosed from 2019 to 2022 were selected from the archives of a veterinary pathology laboratory in São Paulo, Brazil. Tumors were obtained through incisional or excisional biopsies at two different local veterinary dental centers. Inclusion and exclusion criteria were based on access to electronic medical records containing clinical data from the patients, with only non-tonsillar tumors included.

Clinicopathologic Data

Data collected from medical records included breed, age, sex, tumor location, and extent. Microscopically, tumor ulceration, necrosis, and invasiveness were also evaluated.

Tumor Location

The oral cavity was divided into six anatomic locations as follows: (1) rostral portion of the maxillae, extending from the first incisor tooth to the second premolar tooth; (2) rostral portion of the mandible, extending from the first incisor tooth to the second premolar tooth; (3) caudal portion of the maxillae, extending to the second premolar tooth; (4) caudal portion of the mandible, extending to the second premolar tooth; (5) tongue; and (6) oral mucosa and oropharynx, excluding tonsillar tumors. An odontogram was used (25) to indicate the precise location as well as tumor extension.

Tumor staging

TNM staging (26) was performed using thoracic radiographs and abdominal ultrasound or computed tomography. Sentinel nodes were histologically evaluated.

Histopathologic analysis

For microscopic analysis, 3 µm-thick sections were obtained from paraffin blocks, stained with hematoxylin and eosin, and evaluated under light microscopy. Inflammation (intensity and characteristics), necrosis, ulceration, and lymphovascular/blood vessel invasion were investigated. All samples were reviewed by veterinary pathologists, and the previous diagnosis of oral non-tonsillar squamous cell carcinoma was confirmed. Histotypes were categorized according to a previously published classification scheme (25) as conventional/standard, papillary, basaloid, adenosquamous, and fusiform squamous cell carcinomas.

Histologic grading and mitotic count

Histologic grading was performed as previously reported (25). Tumors were categorized as grade I (well differentiated) (Fig. 1A), grade II (moderately differentiated) (Fig. 1B), and grade III (poorly differentiated) (Fig. 1C) by evaluating cell atypia, keratinization, nuclear pleomorphism, and mitotic count (Table 1). Mitotic count was performed by counting mitotic figures within ten representative high-power fields (hot spots), based on previous studies (25).

Inflammation

Inflammatory infiltrates were categorized as absent, mild, moderate, or marked in each tumor based on previously established criteria (3). The predominance of specific inflammatory cells within tumors was also used to characterize inflammation (22).

Statistical analysis

Differences between clinicopathologic parameters (qualitative variables) were analyzed using Pearson's chi-square test. Student's t-test was used to assess the relationship between mitotic count and staging. Kruskal-Wallis and Mann-Whitney tests were used to compare mitotic counts in different anatomic locations (tongue versus mucosa) and inflammation intensity (mild, moderate, or marked). Statistical analyses were performed using GraphPad Prism software (San Diego, CA), version 10.0 for Microsoft Windows. Results were considered significant when $p < 0.05$.

Results

Caseload

A total of 62 cases of canine oral non-tonsillar squamous cell carcinoma was included in this study. Thirty-two dogs (51.6%) were male. Median age was ten years old, varying from five to sixteen.

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Clinicopathologic features and tumor staging

Twenty-two dogs (35.5%) presented tumors which extended to more than one anatomic location. Forty animals (64.51%) had gingival lesions (Fig. 2A), while twelve (19.35%) showed lingual tumors (Fig. 2B), and ten patients (16.14%) had tumors at the oropharynx. Most common locations were 3D and 4E (17.74% each). All tumors were characterized as conventional oral squamous cell carcinomas. Both mononuclear and neutrophilic inflammation were detected within tumors. Lymphovascular and/or blood vessel invasion was not observed within the tumors despite the local invasion. Twenty-one patients (33.87%) were included in stage 2, while forty-one dogs presented as stage 3 or 4 (66.12%). There were no stage 1 patients. Clinicopathologic features are summarized in table 2.

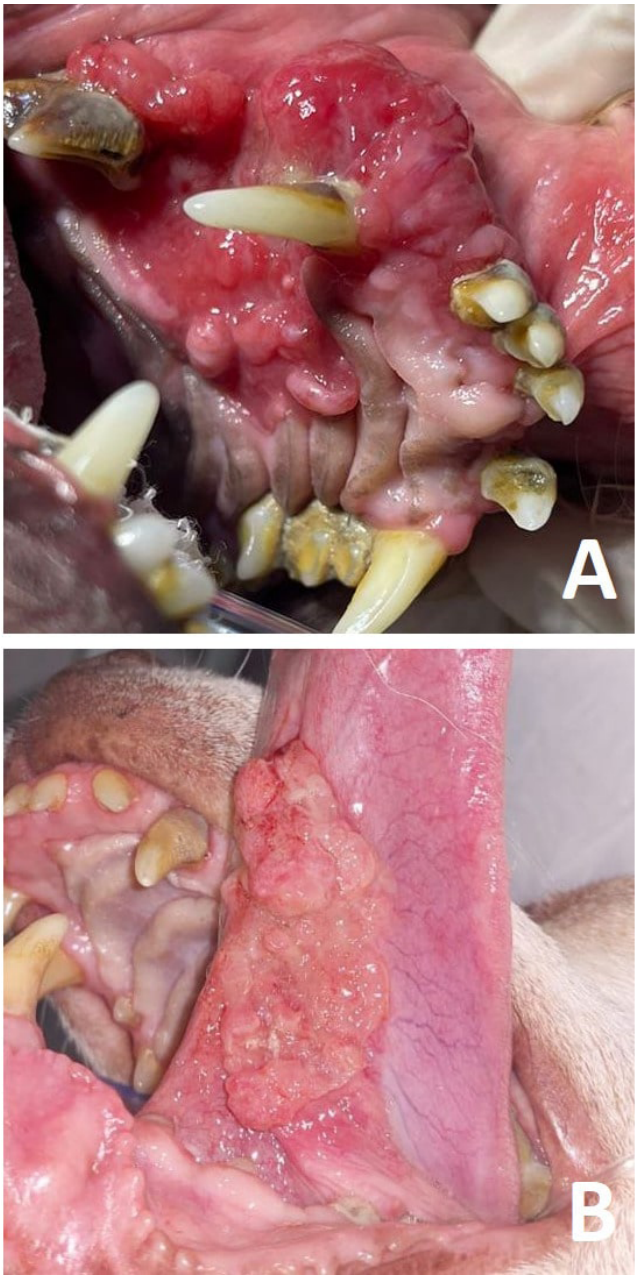

Figure 1. Oral squamous cell carcinomas in dogs. A- Grade I, well differentiated. Keratin pearls were frequent (hematoxylin and eosin, 10x). B- Grade II, moderate differentiation. Occasional keratin pearls were detected and atypia was more frequent (hematoxylin and eosin, 20x). C- Grade III, poorly differentiated. Note absence of keratin pearls and presence of immature cells (hematoxylin and eosin, 20x).

Histologic grading and mitotic count

Thirty-five tumors were categorized as grade I (56.5%), nineteen (30.6%) as grade II, and eight (12.9%) as grade III. The average mitotic count was 21.9. Grade I tumors showed an average mitotic count of 19.11, while grade II tumors revealed an average count of 23, and grade III tumors of 31.3 (table 3). Mitotic counts were higher in grade III tumors than in grade I ($p = 0.0002$) and II ($p = 0.0031$). Relations between histologic grading and other clinicopathologic features are summarized in table 3.

Histologic grading and inflammation

Well-differentiated tumors (grade I) presented less infiltration (mild) in comparison to moderately and poorly differentiated neoplasms. Additionally, mononuclear infiltration score was significantly associated with tumor grading when comparing well-differentiated and poorly differentiated (grade III) tumors ($p = 0.0459$), similarly to what was observed when moderately differentiated (grade II) tumors were compared to poorly differentiated neoplasms ($p = 0.0433$). On the other hand, no statistically significant results were observed regarding neutrophilic inflammation and histologic grading.

Tumor staging and inflammation

A moderate neutrophilic infiltrate was more frequent (80%) in minor staging tumors (stage 2) than in higher staging

Table 1. Microscopic features of oral squamous cell carcinomas according to histologic grading.

Grade	Microscopic features			
	Differentiation	**Keratin pearls**	**Nuclear pleomorphism**	**Mitotic figures**
I	Well differentiated	Present	Mild	Rare
II	Moderately differentiated	Occasional	Moderate	Occasional
III	Poorly differentiated [1]	Absent	Marked	Frequent

[1]Presence of immature cells.

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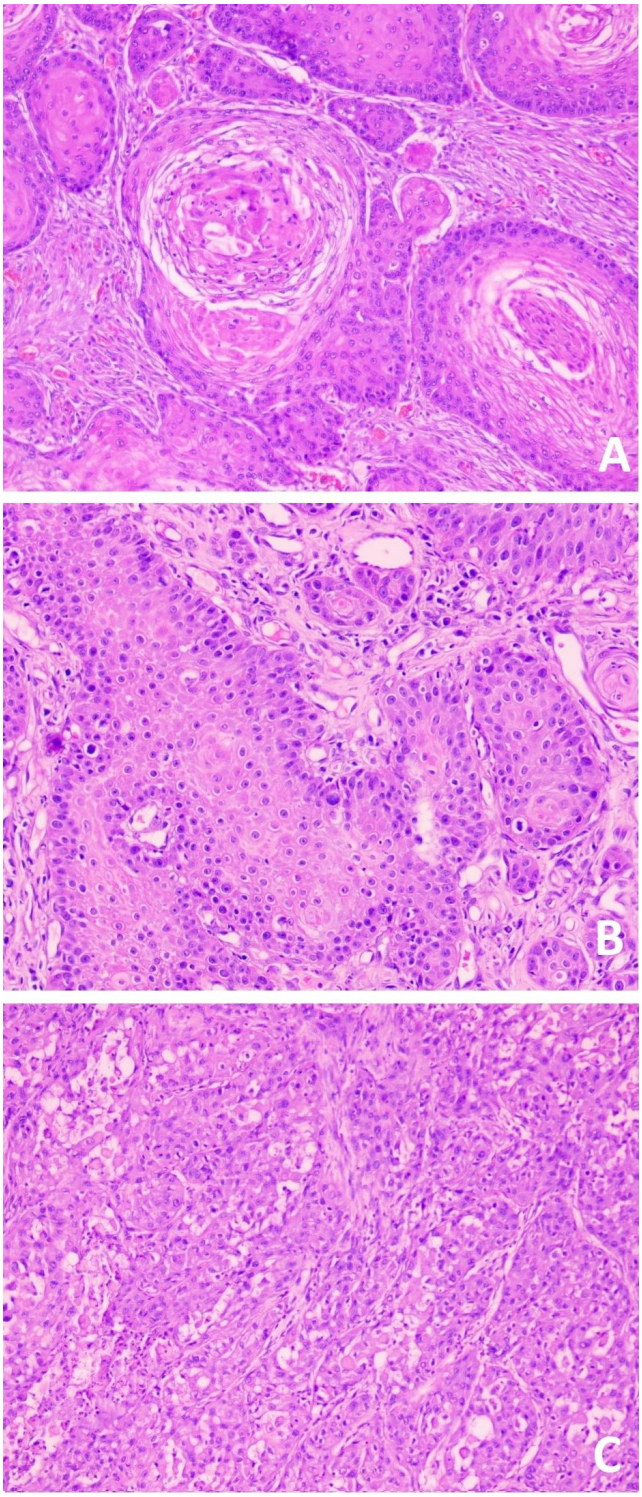

Figure 2. Oral squamous cell carcinomas in dogs. A) Tumor affecting buccogingival mucosa; B) Lingual tumor.

(stage 3-4) neoplasms (56%). Tumor stage and neutrophilic inflammation intensity were significantly associated (p = 0.0498). However, no significant results were observed when evaluating the relation between mononuclear inflammation and tumor staging.

Table 2. Clinical and histopathologic features of dogs with oral non-tonsillar squamous cell carcinomas

	Stage 2	Stage 3 – 4	p value
Age			
< 10 years	11 (52.38%)	12 (29.26%)	0.0746
≥ 10 years	10 (47.61%)	29 (70.73%)	
Sex			
Female	12 (57.14%)	18 (43.90%)	0.3729
Male	9 (42.85%)	23 (56.09%)	
Anatomic location			
Tongue	2 (9.52%)	10 (24.39%)	0.2254
Mucosa	19 (90.47%)	31 (75.60%)	
Necrosis			
Yes	6 (28.57%)	15 (36.58%)	0.5280
No	15 (71.42%)	26 (63.41%)	
Ulceration			
Yes	16 (76.19%)	26 (63.41%)	0.3085
No	5 (23.80%)	15 (36.58%)	
Neutrophilic infiltrate			
Mild	4 (19.04%)	18 (43.90%)	
Moderate	8 (38.09%)	16 (39.02%)	0.0498*
Marked	9 (42.85%)	7 (17.07%)	
Histologic grade			
Well differentiated (I)	14 (66.66%)	21 (51.21%)	
Moderately differentiated (II)	7 (33.33%)	12 (29.26%)	0.0926
Poorly differentiated (III)	0	8 (19.51%)	

*Statistically significant (P<0.05, Pearson's chi-square)

Table 3. Relation between histologic grading, inflammation, and mitotic count

	Grade I	Grade II	Grade III	p value
Neutrophilic inflammation				
Mild	12 (34.3%)	9 (47.7%)	1 (12.5%)	
Moderate	16 (45.7%)	6 (31.6%)	2 (25%)	0.0976
Marked	7 (20%)	4 (20.7%)	5 (62.5%)	
Mononuclear inflammation				
Mild	20 (57.1%)	11 (57.9%)	1 (12.5%)	0.0599
Moderate	15 (42.9%)	8 (42.1%)	7 (87.5%)	
Mitotic count	19.11±8.42	23±6.46	31.88±6.33	0.003*

*Statistically significant (p < 0.05, Kruskal-Wallis test)

Tumor staging and grading

When comparing patients with minor staging (stage 2) and the higher staging (stage 4), no stage 2 tumors (n = 0)

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were poorly differentiated (grade III) while 37.5% of stage 4 tumors were poorly differentiated ($p = 0.0109$).

Discussion

Oral squamous cell carcinomas are among the most common malignancies in humans and dogs (2, 37), comprising 15 – 25% of all canine oral neoplasms (6). Treatment usually involves surgery followed by chemotherapy since radiotherapy is not widely used in veterinary patients (2). Another relevant aspect of canine OSCC is the similarity to its human counterpart, especially in non-tonsillar tumors (37).

In this study, clinicopathologic parameters such as mitotic count, ulceration, necrosis, and inflammation were evaluated and compared with tumor staging and histologic grading. Due to the scarcity of case series available in the veterinary literature, elucidation of these parameters in a larger population is necessary. No stage 1 tumors were observed, and all grade III tumors were staged as 3 or 4. Mitotic count was higher in poorly differentiated tumors. These findings are similar to what was observed by other authors and could be related to cell differentiation and aggressive biological behavior (8, 15, 22, 23, 25).

Of the sixty-two dogs included in this study, 66% were categorized as stage 3 or 4 patients. A higher stage is observed in more than half of dogs presenting oral squamous cell carcinomas, consequently being associated with a worse prognosis (2). Another frequent finding is the tumor's local invasiveness, which is usually accompanied by bone invasion (18). All tumors evaluated showed the same invasive pattern; however, no lymphovascular or blood vessel invasion was detected. This feature may be explained by previous studies (22, 25, 33, 35) that revealed that regional or distant spread is uncommon in oral non-tonsillar squamous cell carcinomas, and their aggressiveness is more associated with local invasion and bone destruction.

The relationship between inflammation and risk in dogs with non-tonsillar squamous cell carcinoma was previously assessed (8). Due to the potential relationship between tumor behavior and inflammation, and the paucity of data in veterinary literature, this study investigated the relationship between mononuclear and neutrophilic intratumoral infiltration and tumor stage and histologic grading.

Histologic grading is related to prognosis in different cancer types, with poorly differentiated tumors usually having a worse prognosis than well-differentiated neoplasms (22). In this series, poorly differentiated (grade III) tumors with lower staging (stage 2) were not available. However, grade I, II, and III tumors were observed both in stage 3 and 4 tumors. This feature could be explained by the generally more aggressive behavior of poorly differentiated tumors.

A statistically significant association between the presence of intratumoral neutrophils and tumor staging was observed, with higher-stage patients presenting less neutrophilic infiltration within neoplasms. Despite this, no relationship between neutrophilic infiltration and histologic grading was observed. On the other hand, mononuclear infiltration was more intense in poorly differentiated tumors and was related to histologic grading, but not to tumor staging. These features may represent characteristics of locally aggressive tumors and are similar to observations by other authors in humans with OSCC (40).

Inflammation is currently recognized as an important hallmark of cancer (11, 12) due to its role in carcinogenesis, tumor growth, progression, and metastasis (1, 21). Consequently, tumor characteristics that can relate inflammation and biological behavior could provide new information that could aid in patient management. In this study, mild to marked neutrophilic and mononuclear inflammation were observed in all tumors and were associated with both tumor staging and grading. Recent evidence shows that neutrophils can participate in the regulation of the tumor microenvironment in both humans (31, 41) and animals (30).

This finding is particularly relevant for oral squamous cell carcinomas, as the oral cavity has a constant neutrophil population in saliva and crevicular fluids in addition to known cells that can be recruited as part of the local defense against pathogens that could reach the digestive tract or originate from oral biofilms (16).

Several studies have discussed the role of tumor-associated neutrophils. Despite this, the diversity of methods used in such studies, variation in design, and the absence of standardized cutoff values can make it difficult to perform a properly analytical and comparative approach to the evidence (4, 9, 27). In this study, it is important to note that the use of paraffin blocks from a single institution, as well as the sample collection method (use of both incisional and excisional biopsies), are among the factors that could influence differences between studies.

In summary, neutrophils may act to restrict tumor cell growth and inhibit metastasis during early tumor development stages by activating cytotoxic T cells, stimulating T cell mitosis (36), or by producing cytokines and growth factors (7). These mechanisms become weakened after tumor progression, and neutrophils then take on other protumoral roles, such as proangiogenic stimulation, aiding in metastasis, and suppressing the local immune response (28, 34, 39).

Additionally, the synthesis of prostaglandin E2 (PGE2) may promote tumor cell proliferation, contributing to the occurrence of additional mutations, as well as ischemic necrosis and ulceration, thereby leading to the recruitment of more neutrophils to the tumor microenvironment. Due to the lack of information in the veterinary literature, the characterization of inflammation in oral squamous cell carcinomas is highly desired. In humans, specific situations, such as periodontal disease, show variations in gene expression when comparing healthy and diseased states (19). Due to differences

in neutrophilic infiltration among different tumor stages, it is possible to suggest an association between neutrophils and tumor cells that may affect their behavior by promoting modifications that increase aggressiveness.

Studies investigating the prognostic role and relationships between tumor cells and other intratumoral factors are encouraged, especially considering the various aspects of inflammation and its association with the tumor microenvironment. Since inflammation was associated with tumor stage in this study, a potential relationship between tumor aggressiveness, based on microscopic analysis and characterization of intratumoral inflammation, can be suggested. This could provide data that could be used to determine risk profiles in animals, thereby aiding in decision-making for each individual patient. Additionally, these findings contribute to the understanding of clinicopathologic features and behavioral differences in canine oral non-tonsillar squamous cell carcinomas.

Conflict of Interest

The authors declare no competing interests.

Ethical

This study was approved by the São Paulo State University Animal Ethics Committee of our institution (CEUA – FMVZ – Unesp, protocol #0579/2023).

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