Metastases from a gingival Squamous Cell Carcinoma (SCC) in a dog

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SUMMARY
This report describes clinical, gross, histological findings and distant metastases from a gingival SCC that mimicked a chronic gingivitis and periodontitis in its early presentation in the right maxillary area of a six year old, male Terrier dog. At necropsy, no maxillary teeth on all over the maxilla were observed and the right maxillary bone was completely destroyed. Greyish-brown or mostly reddish-brown ulcerated and irregular tumoral masses markedly invade this area and the mandible left side. Metastases to lungs, mediastinal lymph nodes, liver, kidneys and cerebellum were evidenced. Histologically, the metastatic and primary masses consisted of islands and cords with many intercellular bridges and intensely eosinophilic keratinized centers with well squamous differentiation. Strongly cytokeratin positive staining of tumoral cells revealed by immunohistochemistry confirmed the epithelial origin of the primary tumour and of its metastases. It was the first report of a well differentiated squamous cell carcinoma with distant metastases to cerebellum and liver in a dog.

Keywords: Squamous cell carcinoma, gingiva, metastasis, cytokeratin, immunochemistry, dog.

RÉSUMÉ
Cette étude rapporte les signes cliniques et histologiques ainsi que la présence de métastases à distance d’un carcinome gingival à cellules squameuses sur un Terrier mâle de 6 ans. Lors de sa première présentation, les symptômes observés évoquaient une gingivite et une péri-odontite chroniques du maxillaire droit. A l’autopsie, plus aucune dent n’était présente sur la mâchoire supérieure et l’os maxillaire droit était complètement détruit. Des masses tumorales irrégulières et ulcérées de coloration gris brun et plus souvent rouge-brun colonisaient fortement le secteur lésé ainsi que le côté gauche de la mandibule. Des métastases dans les poumons, les nœuds lymphatiques médiastinaux, le foie, les reins et le cerebelle ont été mises en évidence. A l’histologie, les masses primaires et métastatiques étaient constituées par des îlots et des travées cellulaires développant de nombreux ponts intercellulaires et dont les centres kératinisés intensément eosinophiles étaient composés de cellules bien différenciées. L’immunohisto-chimie a révélé une forte expression des cytokératines par les cellules néoplasiques qui confirme l’origine épithéliale de la tumeur primitive et de ses métastases. Il s’agit du premier cas décrit de carcinome gingival à cellules squameuses bien différencié capable de donner des métastases cérébelleuses et hépatiques chez le chien.

Mots clés : Carcinome à cellules squameuses, gencive, métastase, cytokératine, immunohistochimie, chien.

Introduction
Oral cancers constitute approximately 2-4% of all malignant tumours in humans [1]. Similarly, malignant tumours of the oral cavity are one of the most common cancer types in the dog, representing approximately 6% of all malignant neoplasms [5]. Approximately 85 to 90% of all oral cancers are squamous cell carcinomas (SCCs) in humans [8] whereas they account for approximately 20% of all tumours in dogs [2]. In humans and animals, tumour prevalence increases with advancing age, and there is no breed or race and gender predilection [11]. Oral cancers seen in dogs share several similarities with the human oral cancers [4, 17, 18, 20]. These similarities include viral and environmental tobacco smoke as risk factors, location-dependent prognoses, and relative resistance to chemotherapy [17]. In addition, these tumours can arise from a variety of anatomic sites (e.g. non tonsillar, tonsillar and lingual) in both humans and dogs [3, 20] and show similar histopathological and biological behaviour [18]. Intra-oral squamous cell carcinoma in dogs and humans can arise from lips, gingiva, tongue, tonsils or buccal mucosa [2, 23]. The most common site of intra-oral carcinoma is tongue in humans whereas the most common site for canine SCC is the gingiva [9, 23].

It has been reported that most SCCs are locally invasive and these tumours are slow to metastasize [4]. The metastatic rate is also low for gingival tumours (10-20%) [2, 7]. In dogs, regional lymph nodes are most commonly affected followed by lungs [12]. Although distant metastases of gingival SCC are rarely seen in humans, they can occur via haematogenous spreading to lungs, pharynx and bone [1]. However, to the authors’ knowledge, distant metastases of gingival SCC other than lungs have not been reported in dogs [12].

This report describes clinical, gross, microscopic findings and distant metastases of gingival SCC in an adult Terrier dog that mimicked a chronic gingivitis and peri-odontitis in the right maxillary area.

Case History
A six year old, a male Terrier dog had been underwent a treatment for chronic gingivitis and peri-odontitis for longer
than one year at a private Veterinary Clinic. The animal exhibited reduced appetite, teeth loss, weight loss and respiratory distress for more than one year. When it was presented for the first time to the clinic of Surgery Department, Faculty of Veterinary Medicine of Erciyes, Turkey, a facial asymmetry and a severe dehydration were also noted.

The treatment procedure (a hemi-maxillectomy) and risk of death at operation because of very poor general clinical condition, and possible post operative complications including, incisional dehiscence, infection, injury to salivary duct, subcutaneous emphysema, mandibular instability, abnormal salivation with secondary chelitis or dermatitis, pain and discomfort, lingual dysfunction, prehension difficulties, ocular problem, cosmetic defects and possibility of the lifelong necessity of tube feeding were explained to the owner. Consequently and because of the deep alteration of the general clinical status of the dog, euthanasia was decided at the owners’ request and the animal was necropsied.

Specimens from various organs including the mass found in the oral cavity, gingiva, lungs, liver, kidney, mediastinal lymph nodes and brain were collected for histopathological examinations. Tissue sections were used for immunohistochemistry by applying the Avidin – Biotin - Peroxidase Complex (ABC) method using primary antibodies directed against cytokeratin (Pan Ab-1 clone AE1/AE3, 1:50, NeoMarkers) [14].

Results

At necropsy, after removal of the cranial skin was removed, no more maxillary teeth were observed and the right maxillary bone was completely destroyed. The deformation extended dorsally to the dorsalis nasi area, caudally to the os frontale and orbita and frontally to the planum nasolabiale. The deformation also reached the left side of the median line. All bone structures in the borderline of this deformation (right nasal bone, facial region of right maxilla, and processus palatinus of right and left maxilla) were destroyed and showed a spongiform appearance. The premolar (PM 1, 2), molar (M 1, 2, 3) and incisors (I 1, 2, 3) were missing on the right lower jaw. Greyish-brown and mostly reddish-brown ulcerated and irregular masses were found in the surrounding of the destroyed area and on the left side of mandible (Figure 1).

Left and right caudal lobes of the lungs did not collapse and showed light grey foci, which have dark red centres. Such structures were also noted on the cut surface of the mediastinal lymph nodes. Moreover, a severe anthracosis was observed in the lungs and in the mediastinal lymph nodes. Few greisy white bulging foci measuring 1-5 mm in diameter were observed on the visceral surface of the liver and on the cut surface of the left kidney. A brownish focus measuring 0.5 cm in diameter was also present on the cut surface of the ventral lobe of the left hemisphere of the cerebellum.

Histological examination of masses from oral cavity and from gingiva revealed large foci with necrotic, keratinous and mineralised centres (Figure 2A). These foci had squamous cell islands which were connected to each other with intercellular bridges. Similar neoplastic cell islands were also detected in the lungs (Figure 2B), mediastinal lymph nodes (Figure 2C), liver (Figure 2D), left kidney (Figure 2E) and cerebellum (Figure 2F). Macrophages of the injured areas presented anthracosis which is characterized by focal accumulation of cytoplasm carbon particle laden alveolar macrophages around the terminal respiratory bronchioles and as clumps within the alveoli, alveolar epithelial cells, in the alveolar septa and interstitial stroma as well as within the cytoplasm of infiltrating mononuclear cells of the lungs, and by sinusoidal macrophages with phagocytosis particles located in the medullar region of the mediastinal lymph nodes and mononuclear cell infiltration was observed around the vessels of the lungs and the kidneys (Figure 2E). Furthermore, prominent haemorrhagic areas into the cerebellum and the meningeal areas were observed. Positive cytokeratin reactions were obtained by immunohistochemistry with all sampled tumoral foci whatever their tissue origin (Figure 3) and confirmed the SCC nature of primitive and secondary tumours.

Discussion

The clinical forms of gingival SCCs are quite variable, exhibiting an ulceration area or an exophytic, granular or verruciform growth, easily leading to misdiagnosis with benign tumours or other inflammatory responses [16]. The similarity of gingival SCCs with periodontal diseases may lead to a delay in diagnosis and poses problems in treatment [22]. In periodontal disease, treatment options change as the severity of disease progresses. The main goal of periodontal therapy is to restore physiologic anatomy of the periodontium and to retard plaque on all tooth surfaces, preventing tissue inflammation, tissue attachment loss, and tooth loss [10]. For this purpose, antibiotic therapy [21], laser therapy [3] for periodontal disease, and cleaning and polishing of teeth, closed root planning, open root planning, sub gingival curettage, gingival surgery, perioceutical therapy, and guided tissue regeneration (GTR) are commonly used [11]. On the other hand, early detection, diagnosis and treatment are
FIGURE 2: A. a well differentiated SCC (white arrows) with keratin pearls (KP) originating from gingiva. Mitotic figures (black arrows). Haematoxylin and eosin. X 400.
B. Islands of metastatic squamous cell carcinoma in lung. Note areas of keratinisation (K), mineralization (M) and irregular tumour islets (arrowheads). Haematoxylin and eosin. X 200.
C. Severe invasion of mediastinal lymph node by tumour cells (arrowheads) separated by bands of fibrous tissue (asterisks). Focal accumulation of cytoplasm carbon particle laden sinusoidal macrophages (white arrows). The lymphoid tissue was markedly reduced: few recognisable lymphocytes (L). Haematoxylin and eosin. X 200.
D. Metastatic squamous cell carcinoma in liver tissue. Note the invasive tumour cells (arrowheads) stimulating stroma fibrosis (asterisks). Haematoxylin and eosin. X 200.
E. SCC metastasis in kidney. Neoplastic squamous epithelial cells (NC) invade the cortico-medullar area. Note the peri-tumoral reactive mononuclear cell infiltration (asterisks) and the presence of poorly recognisable atrophic glomerules (arrowhead). Haematoxylin and eosin. X 400.
F. The cerebellum is nearly completely infiltrated and replaced by cords of well differentiated carcinoma cells. M: Meninges, SA: Substantia alba, SG: Substantia grisea, T: Tumour cells. Haematoxylin and eosin. X 100.
tumours tend to be less invasive and have a low metastatic potential, and maxillectomies depending on the location of tumours [13].

Moreover, the severity of the present case has been probably exacerbated by the long term anti-inflammatory treatment. Poor oral hygiene associated with chronic inflammation may promote the development and invasiveness of oral cancer once the tumoral invasion as indicated earlier [12, 15]. Therefore, in the cases of gingival inflammation, a biopsy would be made for avoiding a misdiagnosis and an abusive exclusion of gingival malign tumours.

In conclusion, to the author’s knowledge, this is the only report recording cerebellar and distant metastases to liver and kidney from gingival SCC in a dog. Consequently, the possibility of carcinoma will be taken into account by veterinary during examination of intra-oral lesions in dogs.

The aetiology of oral squamous cell carcinoma in dogs is unclear [24]. The primary aetiological factor that causes periodontal disease may be bacteria: bacterial products and toxins as well as the body’s own defence mechanisms contribute to the initiation and continuation of periodontal disease [19]. Poor oral hygiene associated with chronic inflammation may promote the development and invasiveness of oral cancer [16]. Therefore, in the cases of gingival inflammation, a biopsy would be made for avoiding a misdiagnosis and an abusive exclusion of gingival malign tumours.

In dogs, SCCs are often localised on gingiva of the rostral mandible and the caudal maxilla [23]. Whereas rostral tumours tend to be less invasive and have a low metastatic potential, caudal tumours tend to be larger and more invasive and produce more often metastases [2]. Although the initial localisation of the primitive tumour has not been determined in the present case, the initial site would be possibly the gingiva of the caudal maxilla: it is a less visible site, often go undetected until it reaches a very advanced stage [12]. It has been reported that only 5-10% of canine gingival SCC metastasizes into regional lymph nodes and only 3% in distant sites [12, 23]. Previous studies in dogs reported distant gingival SCC metastases in lungs and in regional lymph nodes, but not in cerebellum or in abdominal organs such as liver [12]. In the present study, the histopathological findings revealed the cellular characteristics of SCC in the primary site but also in the other injured organs (lungs and mediastinal lymph nodes, liver, kidney and cerebellum). Furthermore, the strongly positive cytokeratin reaction of the neoplastic cells confirmed the epithelial origin of the tumour and metastasis production from the original site. A relationship between poorer tumour differentiation and an increased incidence of distant metastases was reported [4]. A well-differentiated type such as this case is generally considered to have a favourable prognosis [6]. It can be speculated that well-differentiated tumour cells metastasized to distant organs through the lymphatic vessels and blood vessels. However, the presence of cerebellum metastases in the dog would be linked to the complete destruction of the proximal bone structures and the consequent direct implantation of the neo-plastic cells into the meninges.

References


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